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THE PROBLEM OF PREMATURITY
PÆDIATRIC ASPECTS*

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FOR CANADA in 1956,[21] the latest year for which figures are available, 7% of all births were of infants weighing less than 2500 g., of whom one-fifth died, contributing 60-70% of the total neonatal mortality (Table I).[22] The statistics are not significantly different in the United Kingdom.

TABLE I.—CANADA, 1956

	No.	*%*	*Rate per 1000*
Live births	434,932	100	
Premature births	30,200	7	
Infant mortality	13,480		32
Neonatal mortality	8,700		20
Premature mortality	6,090		14

Fig. 1 lists the causes of neonatal death in 527 cases studied in Toronto.[1] On each block, the major proportion is associated with prematurity. Out of the 527, no definite cause of death could be found in 55 who were mostly premature. They probably had biochemical deaths from failure of their internal homœostatic mechanisms: neural, endocrine or renal. Further investigation is required here.

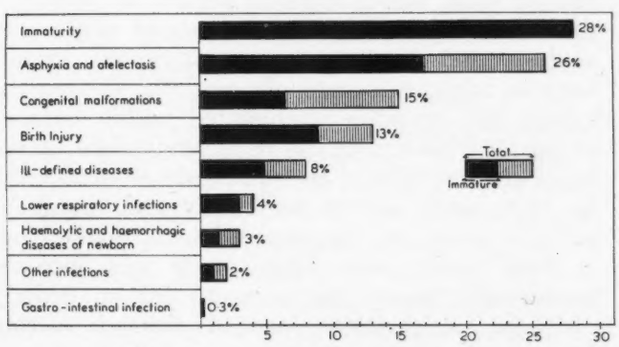

Fig. 1.—Neonatal deaths (according to International Standard Nomenclature of Disease), Toronto study, 1953-1956.

*From the Department of Pædiatrics, University of Toronto, and The Research Institute, The Hospital for Sick Children, Toronto, under a grant from the Department of National Health and Welfare.

In a number of clear-cut categories—birth injury, congenital malformation, blood disorders, infection—although prematurity renders death more likely, a special problem exists which requires specific treatment apart from the condition of prematurity. Broadly speaking, the special hazards of prematurity are pulmonary ones; this large group of conditions we have called abnormal pulmonary ventilation. Atelectasis or incomplete expansion of the lungs accounts for 55%; hyaline membrane disease, next in importance, for about one-third of all cases (Fig. 2).

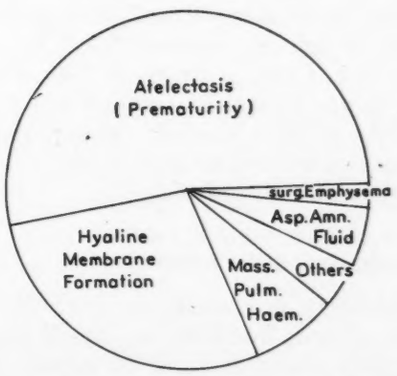

Fig. 2.—Abnormal pulmonary ventilation—Toronto study, 1953-1956.

Table II gives the age at death of those dying primarily of immaturity. The majority died within 24 hours of delivery and 77 out of 83 were dead by the sixth day, so that corrective measures to succeed must be urgently applied. Fig. 3, reproduced from an article by Schlesinger and Allaway, indicates the chance of survival. Mortality falls within each weight group with increasing maturity.[2]

TABLE II.—AGE AT DEATH OF THOSE DYING OF IMMATURITY

Under 1 day	50
1 - 6 days	27
7 - 28 days	3
29 days - 2 months	3
3 - 5 months	—
6 - 12 months	—
	83

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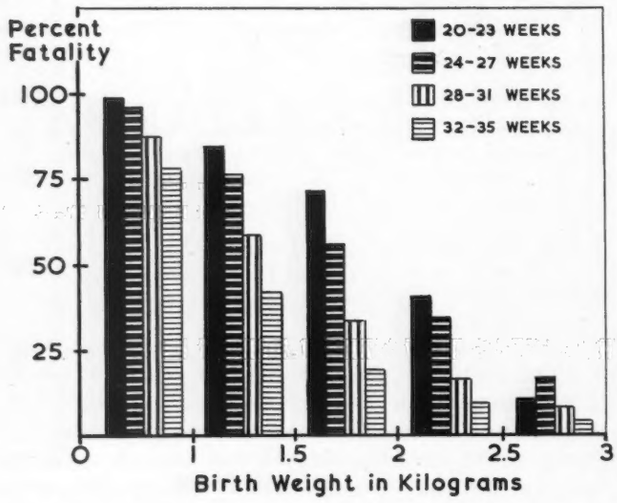

Fig. 3.—Reproduced by permission of the authors and publisher, from the article of Schlesinger and Allaway, "The combined effect of birth weight and length of gestation on neonatal mortality among single premature births" *(Pediatrics,* 15: 698, 1955).

While survival is assured in about 80% of all prematures, many are left with varying degrees of neurological damage. A recent controlled study by Drillien[3] in Edinburgh suggested that two-thirds of 67 prematures of less than 1500 g. had significant neurological defects; Knobloch[4] and her colleagues in the U.S.A. found a figure of 50%. Of her premature group, 8.2% had cerebral palsy compared with 1.6% amongst controls. Mental defect of an important degree was present in 2.6% of probands, compared with 1.6% of controls.

STATEMENT OF THE PROBLEM

The problem of prematurity from the pædiatric point of view is twofold: to attack the approximately 20% mortality, and to ensure that those saved will be useful citizens able to lead a full life.

There is probably an irreducible minimum of fatal cases made up of irreparable birth injuries, intranatal asphyxia and gross malformations. These are prenatally determined, and so are obstetric or genetic rather than pædiatric problems. Most of the remainder of the premature group which presently die are potential survivors and, furthermore, undamaged survivors, if research into neonatal physiopathology brings to light the causes and treatment of the homœostatic failure which occurs when the infant is deprived of his placenta and sterile amniotic bath. The physician of the premature has to try to find a substitute for the placenta and amnion in stabilizing the infant's internal and external environment. Current research is pointing the way to this, and I would like now to discuss new work with therapeutic implications and to speculate as to future developments.

You will recall that 55% of neonatal deaths were associated with incomplete expansion of the lungs. We should, therefore, take a close look at the mechanics of the initiation of respiration.

MECHANICS OF INITIATION OF RESPIRATION

Intra-œsophageal pressure change can be recorded through an indwelling polyethylene tube. This provides us with an indication of intrapleural pressure change, while tidal volume can be measured through a mask and suitable transducer. The pneumotachometer mask illustrated in Fig. 4 is in use in my own laboratory.[5]

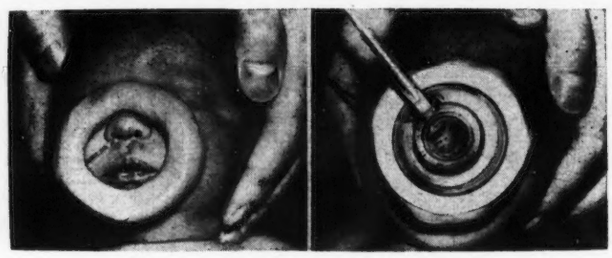

Fig. 4.—Pneumotachygraph in position.

Petter Karlberg[6] from Stockholm has recently recorded intrapleural* pressure and tidal volume of the infant's first breaths. The pressure/volume diagrams in Fig. 5 point out that a negative pressure of the order of 70 cm. of water is developed within the thorax before the first air enters the lungs. The initial gasps last ¼-⅓ of a second and have a volume of about 80 ml. As time passes, lower pressures and volumes are used until the infant settles down to a normal swing of 5 cm. H_2O, with a 15-20 ml. tidal volume.

It is probable that the puny premature with a yielding chest wall is often unable to put forth the muscular effort required to develop this high negative opening pressure. I know of one centre which routinely inflates the lungs of all small premature infants by endotracheal intubation and controlled positive pressure, and I believe this practice has much to commend it, provided the pressure/volume/time characteristics of the normal first breaths are duplicated. Dr. L. Stanley James and his associates[7] in New York have recently demonstrated, from blood chemical studies on neonates, that all infants are born in a state of respiratory acidosis and hypoxia, while depressed infants have an additional metabolic acidosis. In vigorous infants this situation is corrected within minutes of the first breath. In the depressed infant, if the lungs are not inflated spontaneously or artificially, an increasingly severe respiratory and metabolic acidosis develops, characterized by a marked fall in total buffer base, which may soon become irreversible. Hence the necessity for an orderly plan for resuscitation carried through within minutes of delivery if the infant fails to take a spontaneous breath.

RESPIRATORY DISTRESS SYNDROME

The next most important problem numerically is hyaline membrane disease. It is now perhaps

*Measured through an intra-œsophageal catheter.

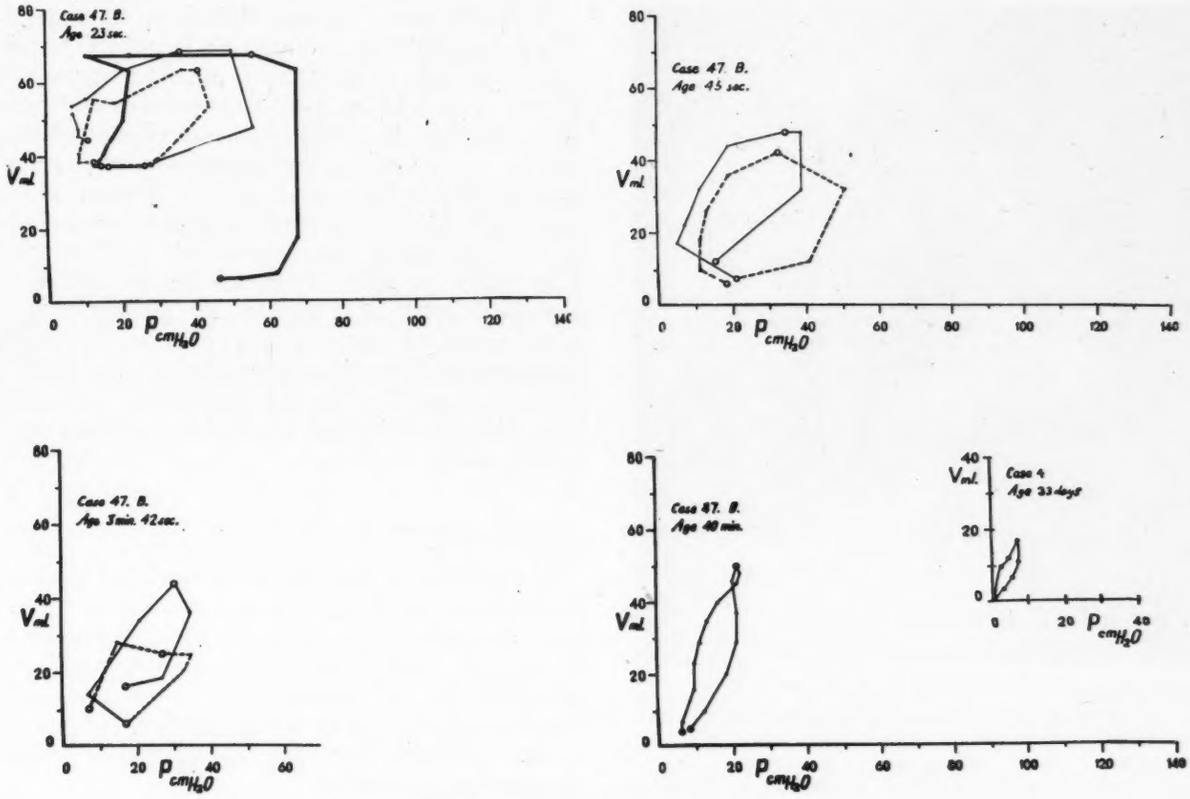

Fig. 5.—Pressure/volume diagrams.

wiser to call this condition the "respiratory distress syndrome", since hyaline membrane formation in the lungs is but one facet of a generalized disease. I cannot help feeling that we are on the threshold of significant discoveries in this hitherto baffling condition. It seems probable now that the basic lesion is the biochemical one of acidosis consequent on birth asphyxia of a pathological degree for which the infant – because of prematurity, acidotic cellular damage or sedation–is unable to compensate rapidly.

It has been established by special histological techniques that the hyaline material in the alveolar ducts contains fibrin and is derived from the infant's own blood.[8] There must therefore be an alteration in capillary permeability or an increase in pulmonary capillary filtration pressure or both. There is evidence for the former in the generalized œdema which occurs simultaneously with body weight loss in the respiratory distress syndrome.[9] In regard to the latter, the relative effects of pH, body temperature, hypoxia and sympathetic amines on pulmonary and systemic pressures, flows, and resistances are currently under intensive investigation. Cardiac catheterization and other studies by Dawes in animals,[10] and by Rowe and James,[11] Mitchell,[12] Eric Burnard,[31] Forrest Adams,[14] and Rudolph and co-workers[15] in infants, have clearly shown that the ductus arteriosus remains functionally patent in the neonate for 24-48 hours after birth, and that this patency is prolonged in the presence of respiratory distress. Initially in the normal newborn infant, blood flows through the ductus in both directions, but within one hour ductal flow is from aorta to pulmonary artery only.[16] It is possible that the period of bi-directional flow exists while full expansion of the lung is being completed.[6] As a result of these changes pulmonary blood flow within a few hours of birth may be as much as twice the systemic flow,[15] although it is frequently less. The relative resistances in the pulmonary vascular bed on the one hand and the systemic vasculature on the other determine the pulmonary arterial and aortic pressures and hence the direction and volume of flow.

In the respiratory distress syndrome of premature infants, three- to fourfold increases in pulmonary blood flow[15] develop owing to a left to right ductal shunt of large volume. At the same time the systemic and pulmonary pressures approximate one another at relatively low levels. By contrast, in some distressed newborn infants, usually in the more mature, the pulmonary vascular resistance increases to such a degree that the pulmonary arterial pressure exceeds the systemic, with consequent reversal of flow, thus augmenting cyanosis of pulmonary origin. Fig. 6 is a venous angiogram from a patient with respiratory distress syndrome showing this reversal of flow with the aorta filling from the pulmonary artery through a patent ductus. Whether these changes in pressures, resistances and flows are direct causes or effects of pulmonary capillary transudation or are only indirectly related phenomena has still to be determined.

While this fundamental hæmodynamic investigation has been going on, there has also been study

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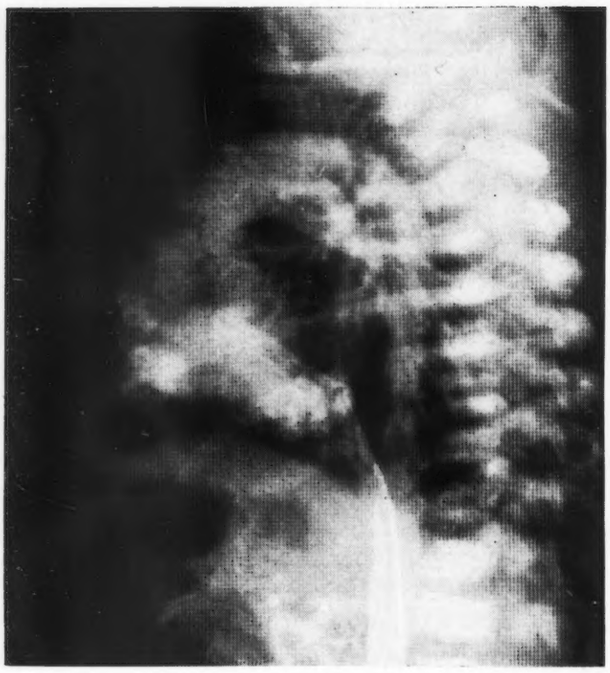

Fig. 6.—Venous angiogram of a patient with respiratory distress syndrome. There is reversal of the usual direction of the ductal shunt. The flow is from the aorta to the pulmonary artery.

of the disordered respiratory physiology. Briefly, the changes in the lung reduce the effective area for gas exchange to such an extent that three or four times the usual volume of air has to be ventilated to maintain the blood gases within viable limits. In addition the lungs may be five times as stiff as usual. This necessitates an approximately tenfold increase in respiratory work, as reported by Cook and associates[17] and confirmed in my laboratory. The sustained high level of work results in exhaustion, eventual respiratory decompensation and death. Perhaps 20-30% of all patients with the respiratory distress syndrome die in this way.

It would seem logical, therefore, to assist the infant artificially to maintain his blood gas homœostasis. It will suggest two possible approaches. Firstly it should be possible, knowing the phase, flow, pressure and volume characteristics of respiration, to take over mechanically the infant's respiration for the critical period. Benson and coworkers,[18] from Göteborg, published three cases in 1958 in which this was successfully achieved. The other possible approach is to utilize the umbilical cord as a means for adding a pump oxygenator to the infant's circulation. Animal developmental work is going on in this field. In both cases monitoring and intravenous adjustment of acid/base, fluid and electrolyte balances would be necessary.

CONCLUSIONS

It seems to me that we are now at the hard core of the problem of neonatal and premature survival, and that unless we apply the new techniques of investigation and control which are becoming available, we shall not make much further headway in improving mortality or salvage figures. I should like to end with some futuristic speculation on possible therapeutic approaches.

The development of rapid physical methods for determination of blood pressure, CO_2 tension,[19] oxygen tension[20] and pH suggests the possibility of regulating therapy continuously, in conformity with the infant's requirements, either manually or by suitable electronic feed-back systems. It would seem that body temperature is of considerable importance hæmodynamically[13] and probably in metabolism. Could not a rectal thermistor be used to regulate the temperature of the incubator through a suitable thermostatic device, rather than

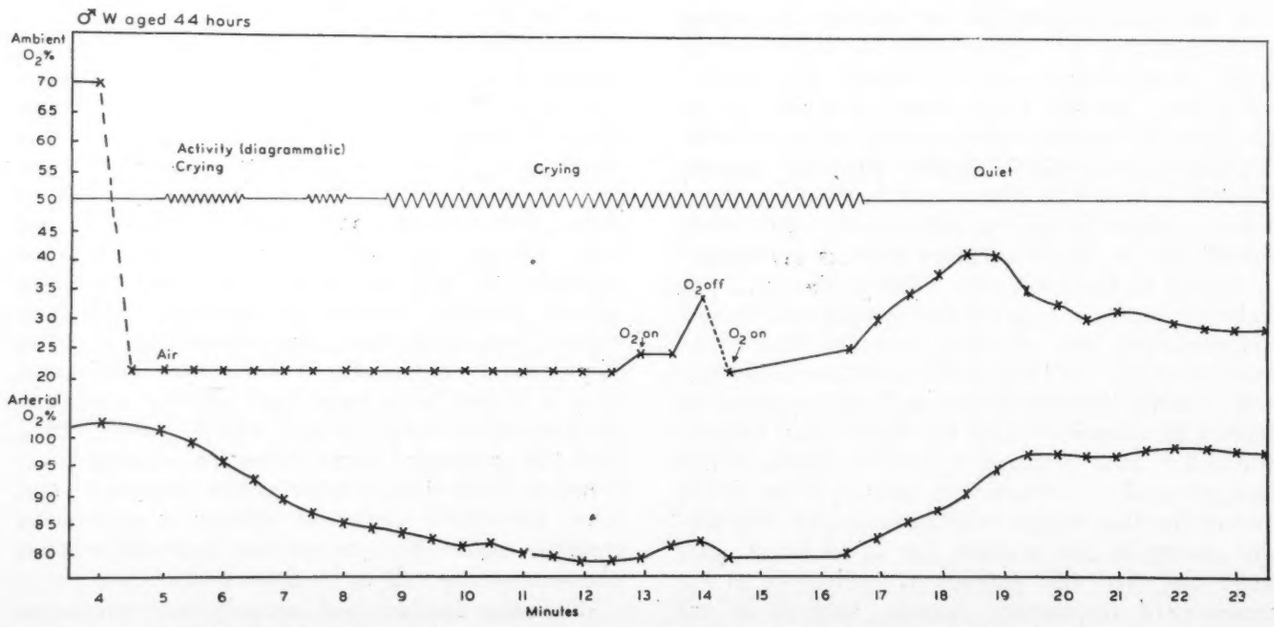

Fig. 7.—The effect of changing environmental oxygen concentration on arterial saturation, as measured by the ear oximeter.

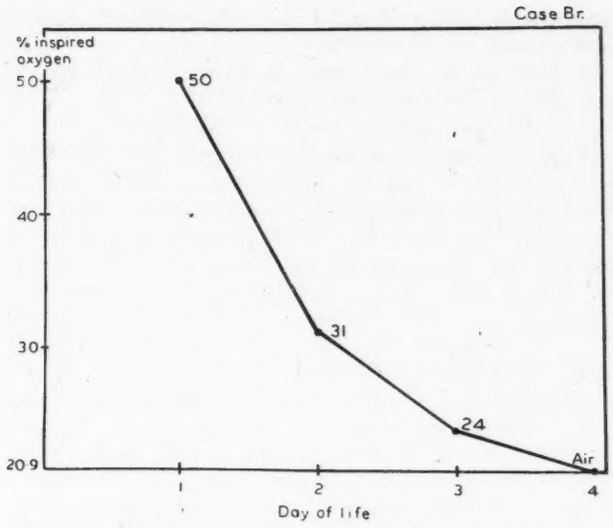

Fig. 8.—This graph illustrates the daily reduction in inspired oxygen concentration for normal arterial oxygen saturation during recovery from the respiratory distress syndrome. (By permission of Dr. Petter Karlberg.)

setting it within rather arbitrary limits as at present? It should also be possible to design a weighing cradle within an incubator which would permit of continuous or repeated weight estimation for the control of fluid balance.

Oximetric determination of arterial oxygen saturation is now practical to a fair degree of accuracy.[21] Could we not use the output from such an instrument to control automatically incubator oxygen concentration? Fig. 7 shows how arterial oxygen saturation varies with the inspired oxygen concentration of an infant in respiratory distress; Fig. 8, the percentage of inspired oxygen necessary to achieve 95% arterial saturation during recovery from the respiratory distress syndrome. The usual incubator percentage of 35-40% would have been inadequate at the height of the disease process to ensure normal arterial saturation but would have been superfluous towards the end of the recovery period. A feed-back mechanism linked to the oximeter output could match supply with demand.

Finally, in regard to the problem of infection to which the premature is unusually susceptible, I would remind you that by complicated and very expensive techniques, it has proved possible to raise animals in a germ-free environment. I am not suggesting that this is necessarily desirable for infants, but maybe we could go further in the field of aseptic management than we do now. It is a matter of technology and finance.

Intelligently applied technology and money are now perhaps the keys to the problem. We have reached the stage where new techniques of investigation and treatment are possible, but have not hitherto been widely used because of the limitation of facilities and finance. It is a sad commentary on our civilization that this should be the case, when such comparatively vast sums can be expended in the development of weapons of destruction.

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RÉSUMÉ

L'importance du problème que présente la prématurité au Canada se juge par les chiffres suivants: en 1956, 7% des nouveaux-nés pesaient moins de 2500 g. et le cinquième d'entre eux mourut, contribuant de 60% à 70% du total de la mortalité néonatale. On ne peut expliquer de façon satisfaisante environ 10% de ces mortalités dont la cause est peut-être neurale, endocrine ou rénale. La majorité des autres cas cependant tient à une ventilation pulmonaire anormale. Plusieurs survivants portent les marques de lésions neurologiques. Afin d'éviter tout changement brusque au mécanisme homéostatique du prématuré le médecin doit s'efforcer de créer un milieu qui à la naissance remplacera le placenta et l'amnios.

L'auteur recommande l'inflation artificielle des poumons du nouveau-né à la naissance par intubation endotrachéenne suppléant ainsi l'effort musculaire que l'enfant débile n'est pas encore à même de fournir. La réanimation doit contribuer à corriger l'état d'acidose dans lequel tous les enfants viennent au monde. On sait que la substance qui forme les membranes hyalines contient de la fibrine et qu'elle provient de lésions capillaires des poumons. Dans le syndrome de souffrance respiratoire chez les prématurés il existe une triple ou quadruple augmentation de la circulation pulmonaire causée par un fort courant de gauche à droite dans le canal artériel. Il est possible que les variations de pression qui s'ensuivent soient impliquées dans ce phénomène. Les aires d'échange gazeux sont si diminuées qu'ils en exigent une volume respiratoire trois ou quatre fois plus grand pour assurer la ventilation alvéolaire. Comme les poumons peuvent être cinq fois plus rigides qu'en circonstances normales, il est évident que ce travail dépasse les forces de l'enfant prématuré.

Afin de suppléer à la défaillance respiratoire du nourrisson l'auteur suggère l'application de respiration mécanique. Il se demande si des recherches plus poussées ne permettraient pas, un jour, de relier le cordon ombilical au circuit d'une pompe oxygénatrice. La température du corps semble jouer un rôle prépondérant dans l'hémodynamique et le métabolisme; l'auteur prévoit l'usage d'un thermostat inséré dans le rectum et qui pourrait servir à régulariser la température ambiante de l'incubateur. L'équilibre hydrique pourrait aussi être jugé d'après les variations du poids obtenues par une balance à enregistrement continu. La saturation artérielle en oxygène serait déterminée grâce à l'oxymétrie et enfin, l'application plus rigide des lois de l'asepsie pourrait surmonter, jusqu'à un certain point, les dangers d'infection auxquels le nouveau-né prématuré est si susceptible.

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UROLITHIASIS IN CHILDREN: REPORT OF THREE CASES AND REVIEW OF THE LITERATURE*

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DURING THE NINETEENTH and earlier centuries urolithiasis was a common pædiatric problem as noted by the many reports in the literature. Despite the fact that the present incidence of urinary tract calculi in children is low, this disease still must be regarded as a problem with some pædiatric significance, although the recent literature on this subject has been limited to isolated accounts of individual cases. Three cases of urinary calculi observed recently in the pædiatric department of St. Joseph's Hospital, Toronto, are presented with a review of the current literature.

CASE REPORTS

CASE 1.—R.B., a two-year-old boy, was admitted to hospital with a history of fever for four days and hæmaturia. On questioning the mother closely, it was learned that there had been several bouts of painless hæmaturia over the past five months, which were of a short duration.

On admission, the baby appeared quite ill and lethargic, and was perspiring profusely. There was definite tenderness in the right costovertebral region. His temperature was 104° F. per rectum; pulse rate 180/minute; respirations 36/minute. Blood pressure was 94/51 mm. Hg. His weight was 24 lb. and height 34 inches. The urine contained red blood cells, white blood cells and albumin. The specific gravity was normal, and reaction varied from alkaline to acid on different examinations. Urine culture was negative. Urine concentration test and urine calcium estimations (24-hour) were normal. Hæmoglobin value was 10.2 g. %, red blood cell count 4,500,000/c.mm. and white blood cell count 30,600/c.mm. A blood smear revealed slight hypochromia and microcytosis.

The total blood serum protein value was 7 g. %; albumin fraction 3.65 and globulin fraction 3.35 g. %. The non-protein nitrogen level was 32 mg. %, blood cholesterol 75 mg. %, blood calcium 9.1 mg. %, phosphorus 5.2 mg. % and alkaline phosphatase 23 units. Blood chlorides were 102 m.Eq./l. and carbon dioxide combining power 50.8 vol. %.

Intravenous pyelography revealed both kidney pelves to be larger than normal. On the right side, there were three large calculi; on the left side there was a long stag-horn calculus with a moderate degree of hydronephrosis.

Treatment consisted of surgical removal of the stones, then intravenous fluid and broad-spectrum antibiotic therapy. The clinical course was uneventful. The removed stones were hard, white and facettal, the largest measuring four centimetres in its greatest width. They were mainly inorganic and contained ammonium and calcium phosphate, calcium oxalate and a trace of cholesterol.

Follow-up on November 6, 1959, showed no recurrence of the condition in 4½ years.

CASE 2.—P.K., a three-year-old girl, was admitted to hospital with a history of painless hæmaturia which recurred periodically for a month before admission. On admission, there was no sign of any discomfort or illness. Her temperature was 99.2° F. per rectum; pulse rate 108/minute; respirations 26/minute, and blood pressure 102/55 mm. Hg. Her weight was 29 lb., height 37½ inches. The urine contained red blood cells, white blood cells and albumin; specific gravity was normal and repeated urinalyses gave alkaline and acid reactions on different occasions. Urine culture grew *E. coli, B. proteus, Streptococcus fæcalis, Aerobacter aerogenes* and *Paracolobactrum intermedium.* The total urinary calcium value for 24 hours and the urine concentration tests were normal. Hæmoglobin value was 12.9 g. %, red blood cell count 4,500,000 cells/c.mm. and white blood cell count 6100/c.mm. A blood smear was normal. Total serum protein level was 6.65 g. %: albumin fraction 4.65 and globulin fraction 2 g. %. Non-protein nitrogen value was 16 mg. %, cholesterol 195 mg. %, blood calcium 9.1 mg. %, phosphorus 5.4 mg. %, and alkaline phosphates 12 units. Blood chloride level was 103 m.Eq./l. and the carbon dioxide combining power 50.4 vol. %.

Intravenous pyelography revealed that both kidneys concentrated the dye promptly. There was, however, a delay in the drainage of the dye from the left kidney pelvis, and evidence of hydronephrosis. The lower portion of the left ureter was visualized and appeared to be dilated as compared with the right side. Two irregular-shaped calculi were seen in the left kidney pelvis.

The two stones were removed surgically, and the patient made an uneventful recovery. The stones were chalky in consistency and grey-white in colour. Chemically, they contained ammonium and calcium phosphate, sulfonamide and a trace of calcium oxalate.

The patient has had periodic bouts of cystitis but no evidence of stone formation since (18-month follow-up; intravenous pyelography, August 1959).

CASE 3.—P.C., a 12-year-old girl, was admitted to hospital because of a sudden onset of colicky abdominal pain which began two hours before admission. She appeared acutely ill on admission, and had marked tenderness in the right costovertebral region. Her temperature was 100° F. per rectum; pulse rate 104/minute; respirations 22/minute. Blood pressure was 110/70 mm. Hg. Her weight was 69 lb. and height 49 inches.

The urine contained red blood cells and albumin; specific gravity was normal. Repeated urinalyses gave alkaline and acid reactions on different occasions. Urine culture was negative. The total urinary calcium value for 24 hours and the urinary concentration tests were normal.

The hæmoglobin was 11.2 g. %, white blood cell count 8000/c.mm. and red blood cell count 4,020,000 per c.mm. Blood smear was normal. Total serum protein value was 6.3 g. %; albumin fraction 3.5 and globulin 2.80 g. %. The non-protein nitrogen was 38 mg. %, cholesterol 180 mg. %, blood calcium 10.6

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*Three case reports from the Department of Pædiatrics, St. Joseph's Hospital, Toronto.

†Department of Pædiatrics, Freedmen's Hospital, Washington 1, D.C., U.S.A.; formerly Resident, St. Joseph's Hospital, Toronto.

mg. %, blood phosphorus 4.7 mg. % and alkaline phosphatase 15 units. Blood chlorides were 105 mEq./l., and the carbon dioxide combining power was 52 vol. %. Intravenous pyelography revealed a right-sided hydronephrosis and a hydroureter involving the whole of the right ureter. No obstructing lesion was demonstrated. Within 24 hours of admission, following a severe attack of renal colic, a stone was passed. The patient was discharged home improved.

The specimen consisted of a spheric stone, which was hard in consistency and yellowish-brown in colour, and measured 0.3 cm. in diameter. It contained calcium phosphate and sulfonamide.

There has been no recurrence in the 18 months since admission (last examination, November 6, 1959).

GENERAL DISCUSSION

At the beginning of this century Bokay[1] collected 1826 cases of urinary stones in infants and children under 15 years of age but most of these were from other continents. The paper of Thomas and Tanner[2] contains the first large series in North America, based upon 203 cases collected through a questionnaire sent to a number of urologists.

Although the peak incidence occurs in patients under the age of four years,[3, 4] calculi have been found at all ages and even in fetuses.[5]

Sex has not been found to be an important factor, except for vesical stones, where the incidence is higher in the male with a proportion of 3 to 1.[3]

Familial influences are probably of no importance except in cystinuria, familial oxaluria and idiopathic hypercalciuria, in which the hereditary nature is recognized.

Racial considerations are of questionable importance. Geographical influences are probably not important, except for consideration of hydroclimatologic conditions. The incidence of stone formation is higher in hot and dry climates[6] where night and day temperature is very high. The inhabitants losing excessive fluid through perspiration void at long intervals and pass a very concentrated urine from which the precipitation of crystalloids may readily occur.

Socio-economic factors play an important part, as evidenced by the fact that among children of the extremely poor families the incidence of urinary calculus formation is much higher than among children of "well-to-do" families. Thomson[7] found calculous disease to be three to four times more frequent in clinic patients than in privileged children.

The common chemical constituents of human renal stones are calcium, phosphorus, oxalate, magnesium, ammonium, cystine and uric acid.[8]

At the present time stones in children not only differ in incidence from that noted in older reports, but also in character.[4] Previously urolithiasis was thought to be endemic, and calculi were found then mostly in the bladder. Recent reports are of geographically isolated cases, and the kidney pelvis and ureter are as frequent sites as the bladder. In the non-endemic series reported in Europe by Winkel Smith,[3] a high percentage of stones were composed of calcium oxalate, whereas in Myers'[4] series from England a high proportion of the stones were phosphatic calculi. On the other hand, in Campbell's[9] cases in the United States, the majority of stones were composed of uric acid and its salts. A small percentage are cystine calculi, the result of metabolic defect which allows the urinary excretion of cystine. The remaining ones are composed of calcium phosphate or calcium magnesium phosphate. These latter types are found in conjunction with urinary tract obstruction, with or without infection. Oxalate stones are more apt to occur without infection, while phosphatic stones are likely to be found with urosepsis, especially if a urea-splitting organism is present.

Etiological Classification

A cause for stone formation can be found in at least half of the patients with urolithiasis.[10] It appears that many factors may be associated with the formation of renal calculi and no single etiologic agent can be held accountable as the single factor common to every type of calculus.

I. Congenital anomalies: Hydronephrosis, congenital ureteric dilatation, horseshoe kidney, calyceal diverticulum.
II. Errors of metabolism: (1) Cystinuria.[11] (2) Familial oxaluria.[12-14] (3) Hypercalciuria[10] (hyperparathyroidism,[15] immobility, excessive milk, alkali, or vitamin D, renal tubular acidosis[16]). (4) Xanthine.[17] (5) Uric acid.[18]
III. Recumbency and immobilization.[19, 20]
IV. Urinary stasis and obstruction.
V. Urinary infection.
VI. Disturbances of the protective mechanism of the colloids.[21]
VII. Vitamin A deficiency.[21]

Pathogenesis

The formation of urinary calculi is a complex process requiring two distinct substances, the colloid and the crystalline. In the presence of obstruction, stasis and infection, it is not difficult to account for the formation of calculi on a simple physical basis.[22] A nidus is formed from a clump of epithelial cells or bacteria. In the presence of an alteration of hydrogen ion concentration, precipitation of crystalloid material is initiated on the nidus. In this connection Higgins[21] and others have pointed out that deficiency of vitamin A leads to hyperkeratinization of the urothelium and increased formation of potential stone nuclei and urolithiasis. This factor may be more important in urolithiasis in children compared to adults.[23] The etiology of calculi which form in the absence of other urinary pathology does not lend itself as easily to explanation. Burkland[24] has proposed that urolithiasis in this group might be explained

by a temporary or permanent derangement of normal metabolic processes which influence crystalloid excretion. Recently Butt *et al.*[21] observed that the urine is a highly saturated solution because of the presence of certain colloids. They stressed the protective action of the urinary colloids as of prime importance in preventing the precipitation and agglutination of crystalloids, and suggested that if the concentration of such protective colloids was not sufficient, stone formation might ensue. In stone-forming patients this colloid is absent and clumping of the crystalloid material is found. Clinically they observed that the subcutaneous injection of hyaluronidase creates a pronounced increase and restoration of the protective urinary colloids of such persons and prevents recurrence of calculi, regardless of composition, in children as well as adults. The enzyme acts on the ground substance of the subcutaneous tissue, the degradation products appearing in the urine as protective colloids. The clinical application of this trial therapy has revealed several limitations.[22]

The largest group of urinary calculi in infancy and childhood is composed of uric acid and its salts. Etiologically they have largely a nutritional basis which is usually accompanied by an elevated blood uric acid level.[9] Recent studies[18] on this subject gave rise to the thought that the insolubility of uric acid in an acid urine, rather than increased urinary uric acid excretion, accounts for the formation of uric acid stones, and that the persistently acid urine may be due to a selective defect in ammonia formation.

Another point of consideration is the widespread administration of sulfonamides. Engel[25] cited evidence that the sulfonamide crystals exert a toxic and deleterious effect on the distal tubules and may cause anuria, due to upper urinary tract blockage.

Diagnosis

A history of hæmaturia, backache or episodes of unexplained hyperpyrexia suggests the possibility of urolithiasis. Hæmaturia in an otherwise fit child calls for a full urological investigation and in this way diagnostic delays will be avoided;[26] hæmaturia is present in 57% of the cases in children.[27] Renal colic is present in 41-54% of the cases.[28] Systemic symptoms are the result of obstruction and infection.

The diagnosis of urolithiasis in childhood should not present great difficulties, and although the condition is now seen only infrequently, it is important that delay should not occur. Failure to recognize the condition may lead to chronic ill health and irreversible renal damage.

A roentgenogram of the abdomen rarely reveals a stone in children. If a stone is suspected on an intravenous pyelogram, retrograde pyelography and/or cystoscopic examination may also be necessary to establish the diagnosis.

The diagnostic requirements form a triad: the diagnosis of urolithiasis, the diagnosis of the underlying lesion (when possible), and the anatomical state of the urinary tract and total renal function.[4]

Treatment and Prognosis

Prophylaxis in urinary stone disease lies chiefly in encouraging a large fluid intake to reduce the concentration of urinary crystalloids, a large vegetable intake for vitamin and anti-constipation factors, and the eradication of urinary stasis and/or infection. Seriously impaired kidneys do not form primary stones because the crystalloid content of their excretion is extremely low.

Specific treatment depends on the size and the site of the stone, the concomitant extent of obstruction and infection, and demonstrable renal damage. For removing multiple calculi and dendritic stones, radiography at the operating table is of invaluable aid in informing the surgeon of the completeness of his efforts.

The prognosis of urinary stone disease depends on the degree of renal damage, the nature and severity of coexisting infection, the size and location of the stone, the promptness and accuracy of diagnosis and the adequacy of treatment.

Today antibiotics and specific chemotherapeutic agents have greatly reduced the surgical mortality, to under 4%. Recurrence of stone formation occurs in about 15% of all patients after surgical removal of the stone. Infection and obstruction are the dominant factors, and particularly when ammoniogenic organisms are present. Generous fluid, high vitamin and, at times, limited calcium intakes[20] are recommended in prevention. At the time of operation the correction of any underlying congenital anomaly should be carried out.

SUMMARY

Three cases of urolithiasis in children are reported. Calculous disease in infants and children occurs frequently enough to be included in the differential diagnosis of many atypical childhood illnesses. Persistent pyuria, hæmaturia and pain along the urinary tract are outstanding indications for complete urological investigation. Thus, urological disease recognized early and properly treated will alleviate much suffering and save many kidneys and some lives.[9] Primary therapy is usually surgical, but medical management is important and directed against recurrence.

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RÉSUMÉ

La lithiase rénale chez les enfants se présente assez fréquemment pour faire partie du diagnostic différentiel de plusieurs affections atypiques de l'enfance. La pyurie rebelle, l'hématurie et la douleur le long des voies urinaires sont des indications manifestes à un examen urologique complet. Les troubles urologiques ainsi reconnus d'emblée et traités correctement soulageront beaucoup de souffrance, épargneront plusieurs reins et quelques vies. Le traitement primordial est habituellement la chirurgie mais la prévention des récidives est importante et relève de la médecine. Les auteurs citent en exemple les trois cas suivants:

Un garçonnet de deux ans présentait de la fièvre, de l'hématurie et une sensibilité dans la région costo-vertébrale droite. La culture de l'urine ne fournit aucune croissance. Le pyélogramme endoveineux montra trois gros calculs à droite et un long calcul coralliforme à gauche avec hydronéphrose. On les enleva tous et les suites furent heureuses puisque le malade s'est toujours bien porté depuis l'intervention il y a quatre ans et demi.

Une fillette de trois ans faisait de l'hématurie depuis un mois. La culture des urines montra une riche flore à base de colibacille, protéus, streptocoque et autres. A la radiographie on découvrit de l'hydronéphrose et un retard dans la vidange du bassinet gauche. Deux calculs furent extraits de l'uretère gauche. Depuis son opération il y a dix-huit mois l'enfant a subi quelques poussées de cystites mais les pierres ne se sont pas reformées.

Une petite fille de 13 ans accusait des coliques depuis deux heures. La région lombaire droite était très sensible. L'urine contenait des cellules rouges et de l'albumine. Au cours d'une colique plus violente que les autres, elle passa un calcul de 0.3 cm. de diamètre à base de phosphate de calcium et de sulfamide. Depuis cet épisode (18 mois) tout est rentré et resté dans l'ordre.

ANTIGENIC RELATIONSHIP BETWEEN POWASSAN AND RUSSIAN SPRING-SUMMER ENCEPHALITIS VIRUSES*

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POWASSAN VIRUS was isolated by McLean and Donohue[1] from the brain tissue of a child who died of acute encephalitis. Immune sera prepared against St. Louis (SLE) virus, and Western and Eastern equine encephalitis viruses, three agents known to exist in North America and capable of inducing a clinical picture of acute encephalitis, were tested by neutralization tests against Powassan virus with negative results. Immune sera against SLE and Murray Valley encephalitis viruses reacted with a Powassan virus antigen in the hæmagglutination-inhibition (HI) test. However, sera against Western and Eastern equine encephalitis viruses failed to react. From the foregoing, McLean and Donohue concluded that Powassan virus belonged in Group B of the arthropod-borne (arbor) viruses, was not SLE or Murray Valley encephalitis virus, and was probably a new agent.

The virus was sent to the Rockefeller Foundation Virus Laboratories, where the above findings were easily confirmed. In addition, an extensive study of the virus was undertaken, the results of which are reported in this paper.

In order to characterize Powassan virus, comparative tests were carried out with 14 Group B viruses. Comparisons were made by HI, complement-fixation (CF) and, to a lesser extent, neutralization tests. The methods for HI have been described.[2] The CF tests were carried out with acetone-extracted brain tissue as antigen and with overnight incubation of the first phase at 4° C. Reference sera were derived from mice repeatedly inoculated (usually five or six times), when sera were desired having a wide cross-reactive spectrum; and from either mice or guinea pigs inoculated only once or twice, when relative specificity was sought.[3]

All viruses with which Powassan virus was compared were previously described Group B agents (for list of references, see Theiler and Casals[4]) with the exception of Li-32 and Modoc viruses. Li-32 is a virus isolated by Beller and Keller[5] from the cerebrospinal fluid of a child suffering from polyradiculitis of the Guillain-Barré type; the virus was sent to Dr. G. Dalldorf, New York State Public Health Laboratory, and by him to our laboratories for identification. The virus received, labelled Li-32, was found to be antigenically closely allied to Russian spring-summer encephalitis (RSSE) virus by CF tests (Casals, unreported work).

Modoc virus was isolated by Dr. H. N. Johnson[6] from the mammary tissue of a wood mouse trapped in California; Dr. Johnson established that the virus belongs antigenically to Group B.

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COMPLEMENT-FIXATION TESTS

Sera from mice repeatedly inoculated with each of 14 different Group B viruses were tested for their capacity to fix complement in the presence of Powassan virus antigen, and several different samples of Powassan virus immune sera were tested against 10 different antigens of the group. All tests were done using increasing two-fold dilutions of sera beginning at a dilution of 1:2 or 1:4, against increasing dilutions of antigen beginning with undiluted antigen or at a dilution of 1:2. With the exception of three viruses—RSSE, Li-32 and SLE—none of the Group B viruses cross-reacted with either Powassan serum or antigen. Immune sera with homologous titres of 1:64 or 1:128 against the Rio Bravo strain[7] of the bat salivary gland (BSG) virus, and against the Bussuquara, dengue Type 2, Ilhéus, Japanese encephalitis (JBE), Modoc, Ntaya, SA H 336, Wesselsbron, West Nile and yellow fever viruses failed on repeated occasions to react with a Powassan virus antigen which had a titre of 1:256. Similarly, an immune serum against Powassan virus, having an homologous titre of 1:128, failed to react with antigens prepared from the following viruses: BSG, Bussuquara, dengue Type 2, Ilhéus, Ntaya, West Nile and yellow fever. The homologous titres of these antigens were between 1:32 and 1:128.

TABLE I.—COMPLEMENT-FIXATION TESTS WITH MOUSE HYPERIMMUNE SERA

Serum	*Antigen*			
	Pow.	*RSSE*	*Li-32*	*SLE*
Powassan.....	128/256*	32/128	32/128	4/32
Russian SSE...	128/128	512/256	256/256	64/128
Li-32.....	64/128	64/256	256/256	16/32
St. Louis.....	0	8/16	0	512/512

*128/256 = titre of the serum is 1:128 and of the antigen 1:256

In contrast with the negative results described, cross-reactions were found between Powassan virus and RSSE, Li-32 and, to a much lesser degree, SLE viruses. The results of a typical test are shown in Table I. The sera used in this test were derived from mice inoculated three times with Powassan virus and six times with the other viruses. It is readily apparent that a greater overlap exists between Powassan and either RSSE or Li-32 than between the Powassan and SLE viruses. The Powassan virus immune serum with an homologous titre of 1:128 cross-reacted with RSSE and Li-32 at a titre of 1:32, but to a titre of only 1:4 with SLE. RSSE immune serum with an homologous titre of 1:512 reacted to a titre of 1:128 with Powassan and 1:64 with SLE. Li-32 immune serum with a titre of 1:256 against its own antigen reacted to a titre of 1:64 with Powassan antigen, but only to 1:16 with SLE. The SLE immune serum with an homologous titre of 1:512 did not react with Powassan antigen. Conversely, Powassan antigen had with both RSSE and Li-32 sera a titre only one-half its homologous value; with Powassan virus serum, the titres of RSSE and Li-32 antigens, both 1:256, were likewise only half the homologous value. Powassan antigen failed, however, to react with SLE serum. Moreover, the titre of SLE antigen with a Powassan serum was 1:32 as compared with a titre of 1:512 with SLE serum, or in other words, 1/16 the homologous value.

TABLE II.—COMPLEMENT-FIXATION TESTS. DISTINCTION BETWEEN POWASSAN AND RUSSIAN SPRING-SUMMER ENCEPHALITIS VIRUSES

	Serum		*Antigen*	
Virus	*Animal*	*Injections*	*Pow.**	*RSSE*
Powassan	Mouse	2	32/128	0
	Guinea pig	2	128/128	16/16
RSSE	Mouse	5	16/64	128/256
	"	5	16/32	64/256

*Footnote as in Table I.

Marked cross-reactions between RSSE and Powassan viruses by CF test were found in nearly all instances; however, differentiation between the two agents was not difficult, particularly when fewer inoculations were given to the animals supplying the immune sera. Table II gives the results of several titrations in which the homologous serum titres are seen to be consistently greater by four-fold to eight-fold than the heterologous ones.

HÆMAGGLUTINATION-INHIBITION TESTS

The results of HI tests consistently showed a higher cross-reaction between Powassan virus immune sera and RSSE antigen than between these sera and any other antigen against which they were tested. The tests also showed that RSSE virus immune sera reacted against Powassan antigen with titres higher than those of immune sera against other Group B viruses, the latter having homologous titres similar to or even higher than that of the RSSE serum.

Table III gives the results with sera from mice repeatedly inoculated. Powassan virus immune serum, after three injections, cross-reacted strongly with RSSE antigen, but poorly or not at all with the remaining antigens. Conversely, of all the immune sera listed in the table having, with one exception only, homologous titres equal to or higher than 1:2560, RSSE serum showed the highest cross-reaction, 1:160, with Powassan antigen. The other sera consistently reacted with this antigen to titres of 1:40 or lower. It can also be seen in the table that Modoc virus presented generally a greater degree of cross-reactivity with other members of the group, Powassan virus excepted, than did Powassan virus. In fact, the antigen derived from the latter was characterized by its low capacity to cross-react with Group B immune sera.

TABLE III.—HÆMAGGLUTINATION-INHIBITION TESTS. SERA FROM MICE REPEATEDLY INOCULATED

Serum		*Antigen*						
Virus	*Injections*	*Pow.*	*RSSE*	*SLE*	*BSG*	*Il.*	*D2*	*Modoc*
Powassan	3	*320	160	20	0	0	0	
Russian SSE	6	160	5120	640	1280	640	320	160
St. Louis	6	40	1280	10,240	1280	1280	640	640
Bat SG	5	40	320	2560	>5120			320
Ilhéus	6	40	320	640	640	5120	640	320
Dengue, Type 2	6	20	320	640	640	320	2560	
Modoc	3	40	320	1280	1280		160	>5120
Japanese	6	40	320	5120	1280	1280	640	320
Bussuquara	3	0	20	80	40	40		0
SA H 336	6	0	40	320	160			80

*320 = The titre of the serum was 1:320. 0 indicates no inhibition at dilution 1:10. The homologous titres of the following immune sera were: Japanese encephalitis, higher than 1:5120; Bussuquara, 1:320; and SA H 336, 1:2560.

Table IV gives the results of tests with sera from guinea pigs and mice inoculated once. The titres of the Powassan serum against Powassan, RSSE, SLE and BSG antigens represent the geometric mean titre of four different samples taken at various intervals after inoculation; the remaining titres in the table represent single observations. Modoc virus immune sera 1 and 2 are from the bleedings of one animal taken at seven and 14 days respectively after inoculation. Table IV shows that Powassan virus immune sera had a higher titre against RSSE antigen than against the remaining ones and that RSSE serum was the only one that cross-reacted with Powassan antigen; thus, these observations supported the evidence given in Table III.

TABLE V.—NEUTRALIZATION TESTS WITH MOUSE HYPERIMMUNE SERA

Serum	*Virus*		
	Powassan	*RSSE*	*SLE*
Powassan	1000*	60	30
Russian SSE	110	300	12
St. Louis	8	6	1000

*Neutralization index value.

It will be observed that, on the basis of accepted criteria of significance for neutralization tests, the Powassan virus immune serum, having an NI of 1000, gave a minimum of significant neutralization against RSSE virus but failed to protect significantly against SLE virus. The RSSE immune serum, with a homologous NI of 300, had an NI of 110 against the Powassan virus and no significant protection against the SLE virus. Finally, the SLE immune serum failed to react with either the Powassan or the RSSE virus. The results of the neutralization tests were, therefore, in accord with those of *in vitro* tests in showing a definite antigenic proximity between RSSE and Powassan viruses.

TABLE IV.—HÆMAGGLUTINATION-INHIBITION TESTS. SERA FROM GUINEA PIGS AND MICE INOCULATED ONCE

Serum		*Antigen*							
Virus	*Animal*	*Pow.*	*RSSE*	*SLE*	*BSG*	*Il.*	*WN*	*JBE*	*Modoc*
Powassan*	GP	160	50	30	20	0		0	0
RSSE	GP	40	640	320	320	80			0
St. Louis	GP	0	0	2560	40	0			0
Bat salivary gland	M	0	20	80	320	20			0
Ilhéus	GP	0	10	40	20	320			0
West Nile	GP	0	20				640	40	
Japanese	GP	0	10	160	160			1280	0
Modoc 1	GP	0	0	0	10	0			320
Modoc 2	GP	0	10	40	160	10			320

*See text for Powassan and Modoc sera; also footnote to Table III.

NEUTRALIZATION TESTS

The results of both *in vitro* tests showed a definite relationship between Powassan and RSSE viruses. Whether a cross-reaction could be detected by neutralization tests was next investigated.

The sera used in the tests were from mice inoculated five times with RSSE or SLE and three times with Powassan viruses; these, as well as the normal mouse control serum, were used in a dilution of 1:2 in normal guinea-pig serum. Mixtures of constant amounts of serum and increasing 10-fold dilutions of virus were incubated at 37° C. for one hour and injected intracerebrally into three-week-old mice. The results of the tests are given in Table V, expressed as the neutralization index (NI) of each serum against the viruses.

DISCUSSION AND SUMMARY

Powassan virus, first reported by McLean and Donohue,[1] has been found by the present work to be a new Group B arthropod-borne virus. The evidence reported in this paper indicates further that this virus is immunologically closer to RSSE virus than to any of the other Group B agents with which it was compared.

The relationship of Powassan virus to the members of the Russian tick-borne complex[8] other than RSSE virus was not investigated, aside from the studies with strain Li-32 which, as received in this laboratory, represents in all likelihood one of the Central European strains of tick-borne encephalitis virus. Consequently, the possibility can be entertained that Powassan virus is identical, i.e., another isolate, with one of the Russian tick-borne complex of viruses other than RSSE and hence not a new virus. This possibility seems unlikely since all the American investigators[9-12] who have studied the antigenic relationships in the Russian tick-borne complex agree that, by every test used, the viruses in this complex are so closely related that differentiation is difficult if not impossible. Pond *et al.*[10] suggested, in fact, that they be considered as strains of one virus.

The relationship between the RSSE and Powassan viruses is not of the same closeness as that reported among the members of the Russian tick-borne complex. Although these two viruses readily cross-reacted in the three types of test used, immunological differentiation between them was not a problem. On the basis of this, therefore, Powassan virus also differs markedly from the members of the Russian tick-borne virus complex not included in these tests.

Although the tests involving the Modoc virus and immune sera were done as part of the effort to characterize Powassan virus, they also supply confirmatory evidence that Modoc virus belongs in Group B and that it is distinct from any of the other agents with which it was compared.

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RÉSUMÉ

Nos lecteurs se rappelleront la découverte publiée dans ce journal en mai de l'an dernier, d'un virus ayant causé la mort par encéphalite d'un enfant de Powassan. Ce virus a depuis fait l'objet de recherches très poussées au laboratoire de virologie de la Fondation Rockefeller. Il fut comparé à 14 autres virus du groupe B au moyen des épreuves de fixation du complément, d'hémagglutination-inhibition et de neutralisation. Les seules réactions croisées observées dans ces épreuves furent obtenues surtout avec le virus de l'encéphalite russe d'été et de printemps, et, à un moindre degré, avec le virus Li-32 et celui de l'encéphalite de Saint-Louis. Le virus Powassan serait donc un nouveau membre du groupe B à vecteur d'arthropode, se rapprochant du virus de l'E.R.P.E. sans toutefois y être identique.

THE SIGNIFICANT PERCENTAGE OF BLAST CELLS IN THE BONE MARROW IN THE DIAGNOSIS OF ACUTE LEUKÆMIA*

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PHYSICIANS AND LAYMEN are aware that once the diagnosis of acute leukæmia is made, a grave prognosis follows, so that no means should be overlooked for proving or excluding such a diagnosis. Most often there is no difficulty in proving the diagnosis, particularly when the peripheral blood examination reveals anæmia, thrombocytopenia, and leukocytosis with considerable numbers of blast cells. Difficulty, however, is sometimes experienced in distinguishing acute leukæmia, especially of the aleukæmic variety, from leukæmoid reactions due to infections, toxins, allergens, or one of many other conditions benign or malignant.[1] Bone marrow examination, therefore, frequently becomes of paramount importance in diagnosis. In the majority of patients with acute leukæmia, a high percentage of the marrow cells will be leukocytic blast forms, but great difficulty arises when a comparatively low percentage of blast cells found in the marrow only suggests the diagnosis of acute leukæmia. As indicated by Dameshek,[2] this is especially likely to occur in children who may respond to infections by means of vigorous leukæmoid reactions, including the presence of sizeable numbers of blasts in the marrow. Blackfan and Diamond[3] have stated that in children the differentiation of acute or chronic infection from malignant neoplasms of the blood may be a matter of the greatest difficulty.

The problem therefore arises as to what constitutes the lowest percentage of blast cells in the marrow which can be regarded as diagnostic of acute leukæmia. As the findings of the following study suggest, when the marrow blast cell count exceeds 6%, acute leukæmia can be diagnosed with a very high degree of accuracy.

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METHODS AND MATERIALS

An analysis was made of 1827 consecutive marrow examinations and accompanying hæmograms performed over a five-year period (1953-57) within the department of hæmatology of the Vancouver General Hospital. Smears and imprints or "squash" preparations were made of the marrow aspirates and these were treated with Wright's stain. A total of 300 nucleated cells was counted on each marrow examination using high power and oil immersion lenses. Blast cells were seldom specifically identified as myeloblasts, lymphoblasts, or monoblasts, because of the difficulty of such accurate identification of the various blast forms.[4-8] As Daland[9] points out, the recognition of the type of blast of the white cell series is usually of academic interest. Others,[10] however, have expressed confidence in the value of differentiating cells of the leukæmic cell series. Phase contrast microscopy[11] has been thought to be useful in the recognition of blast cells as myeloblasts or lymphoblasts. It is assumed, in agreement with many authors, that the majority of childhood cases of acute leukæmia derive from the lymphocytic series. No similar assumption can be made of acute leukæmia of the adult.

The criteria for the recognition of a leukocytic cell as a blast cell[12] were: (1) absence of cytoplasmic granulation, (2) large nuclear-cytoplasmic ratio: tendency towards large nuclei, or scant cytoplasm, (3) finely divided nuclear chromatin, (4) recognizable nucleoli, and (5) basophilic cytoplasm.

RESULTS

The analysis of the first 266 cases (see Table I) revealed that in 180, no blast cells were seen, while in 44 cases, blast cell counts of between 0.0 and 1.0% were recorded. Thus, 224 of the 266 cases had blast cell counts of less than 1.0% in the marrow, and among these 224 cases, 94 were diagnosed as normal hæmatologically and the remaining 130 cases included a considerable number of hæmatological disorders, some of which were iron deficiency anæmia, idiopathic thrombocytopenic purpura, polycythæmia rubra vera, multiple myeloma, erythroid hypoplasia, spherocytic anæmia, chronic granulocytic leukæmia, pernicious anæmia, megakaryocytic myelosis and reaction to infection. In addition, there was one known case of acute leukæmia in complete hæmatological remission with less than 1% blast forms in the marrow. It was readily apparent from this wide assortment of diagnoses that no specific pathological interpretation could be made of marrow blast cell counts up to 1%. There then remained, from the original 266 cases, 42 with marrow blast cell counts greater than 1%. Among these, 28 were proven cases of acute leukæmia and two of these were in a state of remission with blast cell counts of 1.7 and 3.7% respectively. (Previous marrow examinations of these two cases had been diagnostic of acute leukæmia before remission.) In the 26 remaining cases of acute leukæmia, marrow blast cell counts ranged from 9 to 96%; the majority of cases had more than 50% blast cells. Finally, the remaining 14 cases (that did not have acute leukæmia) of the 42 with blast cell counts over 1% consisted of three cases of chronic lymphocytic leukæmia with counts of 1.3%, 2.0% and 2.0% respectively; two cases of pernicious anæmia with blast counts of 1.3 and 1.7%; one case of hyperglobulinæmia purpura with 1.2% blasts, and an important group of eight cases with marrow blast cell counts greater than 2%. In these eight cases (see first eight cases of Table II), blast counts ranged between 2.3 and 5.3% in seven cases, while in the eighth case the blast count was 14.3%.

TABLE I.—ANALYSIS OF THE FIRST 266 MARROW EXAMINATIONS TO SHOW THE PERCENTAGE OF BLAST CELLS (266 REPRESENTS THE TOTAL NUMBER OF EXAMINATIONS FOR A ONE-YEAR PERIOD).

Number of cases	*Percentage of blast cells in the marrow*
180	0.0%
44	0.0—1.0%
42	1.2—96%
Total 266	

Since from this initial examination of the first 266 cases it was apparent that no interpretation was possible of counts below 2%, the provisional normal upper limit for blast cell counts in the marrow was taken as 2%. With this somewhat arbitrary upper limit, it was decided to record among the 1827 cases studied, all cases with blast cell counts greater than 2% in which the diagnosis of acute leukæmia was not established at the time of the initial marrow examination. A total of 53 such cases was recorded (see Table II). Nine of the 53 cases (marked by a single asterisk) were later diagnosed as acute leukæmia. Two exceptional cases, both in infants (Cases 8 and 27), while originally considered likely to have acute leukæmia when first examined, never developed the disease, but to the contrary, both patients are now enjoying normal health—over two years and four years respectively after their marrow examinations. Both cases represented uncommon hæmatological disorders of infancy; one, megaloblastic anæmia of infancy in a five-month-old baby girl, successfully treated with folic acid; and the other, a leukæmoid reaction, presumably due to an allergen or toxin, in a four-week-old baby boy. (Bessis[13] states that leukæmoid reactions can be nothing more than a manifestation of an individual intolerance to a material which is not toxic for the majority of individuals.)

Forty-eight cases are listed in Table II with marrow blast cell counts ranging from 2 to 6%, and five cases with counts over 6%. At the time of the listed counts, the diagnosis of acute leukæmia was not established in any of the 53 cases. Later, nine cases* developed acute leukæmia. The

TABLE II.

Case No.	Sex	Age	% Marrow blasts	Diagnosis on basis of first examination
1	M	17 months	3.0	Idiopathic thrombocytopenic purpura
2	M	17 years	2.3	Chronic lymphocytic disease
3	M	22 months	3.3	Hæmolytic anæmia
4	M	74 years	4.3	Reaction to infection
5	M	69 years	4.7	Myeloproliferative syndrome
6	M	14 years	5.3	Reticulum cell sarcoma
7	F	3 months	5.3	Reaction to infection
** 8	M	4 weeks	14.3	Leukæmoid reaction to allergen
9	M	14 months	2.7	Iron deficiency anæmia
10	F	2 months	5.3	Congenital hypoplastic anæmia
*11	F	54 years	4.3	Pernicious anæmia
*12	F	21 years	5.0	No diagnosis; possible myelosis
*13	M	45 years	2.3	No diagnosis
*14	M	63 years	4.0	No diagnosis; possible myelosis
15	M	3 months	4.0	Idiopathic thrombocytopenic purpura
*16	M	50 years	3.0	Myeloproliferative syndrome
17	F	48 years	3.7	Iron deficiency anæmia
18	F	75 years	5.7	Reaction to infection
19	F	3 months	4.8	Anæmia of prematurity
20	M	43 years	2.7	No diagnosis
21	M	67 years	4.0	Lymphosarcoma
22	M	45 years	4.5	Myelofibrosis
23	F	38 years	5.7	Chronic granulocytic leukæmia
24	M	42 years	4.0	Chronic granulocytic leukæmia
25	M	42 years	3.7	Pulmonary sarcoidosis
26	F	49 years	4.0	Disseminated lupus erythematosus
**27	F	5 months	9.0	Megaloblastic anæmia of infancy
*28	M	19 years	6.7	Promyelocytic leukæmia
*29	F	86 years	9.4	Possible acute leukæmia
30	M	57 years	2.3	Lymphosarcoma
31	M	4 years	3.0	Acquired hæmolytic anæmia
32	F	18 months	5.0	Letterer-Siwe's disease
*33	F	83 years	4.3	Possible acute leukæmia
34	M	71 years	4.3	Monocytic leukæmia
35	M	75 years	3.7	Normochromic normocytic anæmia
36	M	39 years	4.0	Chronic granulocytic leukæmia
37	M	63 years	2.7	Chronic lymphocytic leukæmia
38	F	64 years	4.7	Chronic granulocytic leukæmia
39	M	73 years	4.0	Reaction to infection
40	M	74 years	4.3	Chronic granulocytic leukæmia
41	M	60 years	5.7	No diagnosis (collagen disease)
42	M	56 years	3.7	Lymphosarcoma
43	M	33 years	3.3	Iron deficiency anæmia
44	M	5 years	3.5	Idiopathic thrombocytopenic purpura
*45	M	50 years	13.0	Chronic lymphocytic leukæmia
46	M	63 years	3.0	Hypoplasia; Hodgkin's disease
47	F	31 years	3.7	Idiopathic thrombocytopenic purpura
48	F	85 years	2.3	Myeloproliferative syndrome
49	M	52 years	2.3	Chronic subleukæmic leukæmia
50	M	15 months	2.6	Iron deficiency anæmia
51	M	13 months	5.4	Iron deficiency anæmia
52	F	16 years	3.6	Agranulocytosis; hyperthyroidism
53	F	86 years	4.0	Erythroleukæmia

*These nine cases later developed blast cell leukæmia.
**See text and case histories regarding these two cases.

histories of Case 8** and Case 27** are summarized briefly.

CASE 8.—This four-week-old baby boy was found to have a marrow blast cell count of 14.3%; a white blood count of 38,000 per c.mm. of which 40% were blast cells; a hæmoglobin value of 8.2 g. %; and a platelet count of 31,000 per c.mm. The baby had exhibited a papular and a purpuric rash shortly after birth. The purpuric rash vanished quickly, but the papular rash remained for approximately four weeks. The liver and spleen were not enlarged, and there were no palpable lymph nodes. The infant was vigorously active. After discharge from hospital, at six weeks of age, the baby continued to thrive. The hæmatological diagnosis at that time was probable congenital acute leukæmia. But in view of the child's presently continuing good health nearly three years later, with return of the hæmogram to normal, the diagnosis of congenital acute leukæmia is unlikely. Considering the papular rash at the time of the initial findings, it is thought likely that the marrow blast cell count of 14.3% represented a reaction to some allergen or toxin.

CASE 27.—This five-month-old baby girl presented with pallor and moderately severe anæmia, confirmed later to be megaloblastic anæmia of infancy. The marrow blast cell count of 9.0% aroused suspicions of a leukæmic process. This child was treated successfully with folic acid. She is now four years old and remains very well.

Forty-eight of the 53 cases listed have marrow blast cell counts between 2 and 6%, whereas the remaining five cases have counts greater than 6%, although not higher than 14.3%. Of these latter five cases, three developed acute leukæmia, while the other two (Cases 8 and 27 just described) constitute the outstanding exceptions in the 1827 surveyed. Neither of these two, both infants under six months of age at the time of examination, has developed acute leukæmia, nor is it now expected that this will occur. Both are examples of the extreme reactivity which can occur in the bone marrow of young children. Six of the 48 cases with blast counts between 2 and 6% developed acute leukæmia after the initial examination.

TABLE III.

Diagnosis	Percentage of blasts in marrow	No. of cases
Acute leukæmia	>6%	127
Acute leukæmia	<6%	9
	TOTAL	136

136 cases of acute leukæmia are summarized to show that 127 cases, or 93%, had blast cell counts in the marrow greater than 6%.

A total of 136 cases of the 1827 reviewed were finally diagnosed as having acute leukæmia, clinically and hæmatologically. Only nine of the 136 cases had marrow blast cell counts below 6%, and three of these cases were in remission. Thus, 127 of the 136, or 93% of the cases with acute leukæmia, had marrow blast cell counts greater than 6% (see Table III). When one adds to these 127 cases of acute leukæmia with counts greater than 6%, the two exceptional non-leukæmic cases with counts of 9% and 14.3%, it is found that a total of 129 cases from the 1827 reviewed had marrow blast cell counts greater than 6% (see Table IV). Thus, 127 of the 129 cases, or 98% of all cases in the survey with marrow blast cell counts over 6%, were confirmed cases of acute leukæmia. There were 20 cases of acute leukæmia with blast cell counts in the marrow between 6 and 20%.

DISCUSSION

In a series[14] of 20 normal marrow examinations, marrow myeloblasts ranged from 0.0% up to 5.5%. There are singularly few references to a critical marrow blast cell count relative to the diagnosis of acute leukæmia. Diamond[15] suggests that the presence of more than 20% blast forms in the bone marrow is more typical of leukæmia than of a leukæmoid reaction. In discussing how closely the leukæmoid reaction of tuberculosis could mimic the picture of true leukæmia, Diamond has further emphasized that the presence of true blast

TABLE IV.

Diagnosis	*No. of cases with blasts >6%*
Acute leukæmia.....	127
Leukæmoid reaction (allergy)	1
Megaloblastic anæmia of infancy	1
TOTAL	129

129 cases with blast cell counts in the marrow greater than 6% are summarized to show that 127 cases, or 98%, were patients with acute leukæmia.

forms among the very immature forms is not seen, and was not seen by Sabin and her associates, even in the most active cases of tuberculosis in animals. Hayhoe[16] has stated that cases of pancytopenia which never becomes frankly leukæmic frequently show some increase in primitive cells in the marrow, and as many as 20% of the marrow cells may be blast forms.

Hyman *et al.*[17] include in their criteria of remission of acute leukæmia in response to therapy, absence of cells in the bone marrow that can be individually identified as leukæmic, and reduction in number of blasts to less than 5% of the total nucleated cells for adults and 10% for children.

Using criteria established earlier in this paper, and applying such criteria to the analysis of 1827 marrow examinations, it has been shown that when marrow blast cell counts exceeded 6%, the diagnosis of acute leukæmia was made with a high degree of accuracy. It is not intended to create the impression that all bone marrow examinations with blast cell counts in excess of 6% constitute absolute evidence of acute leukæmia, but rather that these counts strongly support such a diagnosis when difficulty arises in differentiation of acute leukæmia from other conditions, benign or malignant. Clinical findings and peripheral blood studies will often be helpful in establishing the correct diagnosis. Perhaps a critical blast cell count of 6% is of least usefulness in those doubtful cases arising in infancy and early childhood because of the marked reactivity of the bone marrow in them.

Blast cell counts between 2 and 6% remain significant in that while many benign hæmatological disorders produce such counts, acute leukæmia may very well be present either in remission or in an early phase of development. In such instances serial marrow examinations, taken in consideration with the many other hæmatological and clinical features of acute leukæmia, will aid in confirmation.

Marrow blast cell counts from 0.0 to 2.0% are not significant, since such counts are not infrequently observed in the marrow of normal individuals, as well as in many hæmatological disorders.

SUMMARY

Consecutive marrow examinations and accompanying hæmograms were reviewed in 1827 cases in an attempt to establish a percentage of leukocytic blast cells in the marrow above which the diagnosis of acute leukæmia could be made. Marrow blast cell counts greater than 6% constitute strong evidence for the diagnosis of acute leukæmia. Marrow blast cell counts in excess of 6% were found in 129 cases, and 127 or 98% of these proved to be acute leukæmia.

Forty-eight cases (Table I) had blast cell counts between 2 and 6%, and six of these represented acute leukæmia in remission or in an early stage of development. Such marrow blast cell counts therefore demand further careful investigation. Marrow blast cell counts up to 2% allow of no specific pathological interpretation; such counts occur frequently in normal individuals, as well as in many hæmatological disorders.

ADDENDUM

Since the completion of this study, the authors have learned of three adult patients (two cases of myelofibrosis; one case of chronic granulocytic leukæmia) in whom the percentage of blast cells in the marrow was greater than 6%. Not one of these patients has followed the clinical course of acute leukæmia.

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RÉSUMÉ

Dans certaines circonstances, le dépistage de la leucémie aiguë peut ne dépendre que de l'étude du myélogramme. La proportion relative de cellules blanches "blastiques" en est la clé. Les auteurs ont revu l'hémogramme et les frottis de prélèvement de moelle de 1827 malades traités consécutivement dans le service d'hématologie de l'hôpital général de Vancouver. Ils en concluent qu'une proportion de cellules leucoblastiques dépassant 6% forme un indice diagnostique très important puisque des 129 malades qui présentaient cette concentration cellulaire, 127 ou 98% étaient atteints de leucose aiguë.

Parmi les 48 malades dont la proportion de ces cellules s'établit entre 2 et 6%, six étaient des cas de leucémie aiguë à l'état de rémission ou à un stage précoce d'évolution. Une moelle qui présente un tel tableau forme donc une indication sérieuse à une observation plus poussée. Une concentration de moins de 2% ne possède aucune signification pathologique particulière. On la retrouve chez un grand nombre d'individus normaux et aussi dans des désordres hématologiques divers.

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USE OF IMIPRAMINE (TOFRANIL) IN THE AGED CHRONICALLY ILL*

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THE RECENT appearance of imipramine (Tofranil), a new drug with potent anti-depressive properties, has stimulated a great deal of interest in clinicians and in research workers at both the clinical and laboratory level. This new drug has been shown to be the most effective anti-depressant so far available, and there is fairly unanimous experience amongst the first investigators and authors[1-12] that on the basis of their clinical trials, a significant improvement can be expected in from 60% to 80% of cases treated. These results are reported for "uncomplicated" states of depression; the need for electroshock has been obviated in many instances. The specific mode of action has not as yet been established, though speculation has been offered in the absence of scientifically valid data. The drug has had clinical trials in mental hospitals, on psychiatric inpatient services at the general hospital level and also with ambulatory persons as outdoor patients or in private practice.

There is general agreement that the drug is equally effective at all levels, provided appropriate patient selection is carried out. The use of imipramine is indicated for the treatment of primarily depressed states, classical periodic endogenous depression, and the depressed phase of manic-depressive psychosis. The onset of improvement (therapeutic lag) varies from two days to eight weeks or longer. The most frequent side effects are noted to be some lowering of the blood pressure and mild atropine-like effects: dryness of the mouth, haziness, sweating and weight gain. Toxic effects are rare and are to an appreciable extent related to the dosage used, and include rash, cardiovascular effects and jaundice. Most authors have used daily doses of 100 to 150 mg., and find this level therapeutically effective and relatively free of toxic effects. On higher dosage, up to 300 mg. daily, undesirable side effects are seen more often. Mann *et al.*[13] have recently reported some toxic reactions of alarming severity and the rapid development of congestive heart failure in a number of patients; they felt that cardiovascular disease, apart from simple hypertension, was at least a relative contraindication to the use of this drug. At the recent annual meeting of the Canadian Psychiatric Association, several psychiatrists reported verbally the sudden death of patients who were receiving imipramine. Although the drug was suspect in this sudden cardiovascular collapse, no definite correlation was established between the two. However, the need for caution seems well founded until the limits of safety are more firmly established by clinical studies and further investigations.

Thus far, there are only a few scattered references about the use of imipramine in patients with senile depressions or depressions associated with organic lesions, such as cerebral arteriosclerosis and parkinsonism. Cameron[14] in a report on the use of imipramine in the aged comments that it may be of value in the aged in alleviating a rather nonspecific type of mood disturbance when it exists, but, naturally, has no influence on the rapidly progressive organic syndrome.

One of us has already reported his experience with imipramine (Tofranil) in private practice[11] and through continuing and subsequent observation on a larger series can confirm the original impression of it as "the most effective anti-depressant drug that has yet appeared". It appeared worth while therefore to extend the earlier observations to include the special group of chronically ill and aged hospital patients in an attempt to evaluate the effectiveness of the drug on states of chronic brain syndrome. An attempt was also made to evaluate the drug's effectiveness in relieving pain, and its effectiveness in those more complicated depressed reactions associated with or superimposed upon organic disease states, especially where definite cerebral organic deficit exists. The project was undertaken to test the further limits of clinical effectiveness of imipramine, to study the side effects in a group of aged chronically ill patients, and to extend observations on the limits of safe dosage of this new drug.

METHOD AND RESULTS

The present study concerns a group of hospital patients at the Jewish Hospital of Hope, Montreal. The criterion for admission is the presence of chronic illness requiring active hospital treatment; primary states of mental illness *per se* are excluded from admission. The commonest diagnoses include chronic neurological disease, such as parkinsonism, cerebral vascular accidents (hemiplegia) and disseminated multiple sclerosis, diabetic disease with its end states, terminal carcinoma and circulatory disorders (chronic congestive heart failure, chronic hypertensive disease). Most patients are aged (though not all) and present the social problems usually associated with chronic illness and the attendant drains on financial, physical and emotional resources of the family unit. In many patients a depressive reaction has been noted and attributed to the disabled state, to loss of vitality, separation from home, settling into a helpless dependent adjustment and to other factors.[15] Such depressed reactions are either superimposed on the primary disease process, thus complicating the care of the patient, or express themselves rapidly through disintegrative psychic processes to regressed organic psychotic states, which if recognized early and treated, are to some extent reversible. With this

*Tofranil (Geigy Pharmaceuticals).

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type of patient population then, an aged group with a mixture of organic and psychological disorders, clinical trial of imipramine was undertaken.

The patients were evaluated before the use of imipramine. All other drug therapies which might contaminate the experiment were stopped. The drug trial lasted for 12 weeks in the individual patient, longer when any change was noted, and interrupted only by necessity. Daily observations were made by one of the authors; weekly observations including review of mental status, by the other. Ward nurses and the nursing supervisor collaborated with their observations. The special data recorded are concerned with general cooperation, alertness, sleep, feeding responses, affect changes, any change in confusion and disorientation states and effects on pain. Blood pressures, results of urinalysis and hæmograms were recorded regularly. Complications and toxic effects were watched for. The dose administered varied between 75 mg. and 200 mg. daily, the average being 100 mg. daily. Special factors such as the aged state, lowered metabolic processes and complicating disease conditions were taken into consideration in determining the individual dosage and the length of the therapeutic trial. The number in the series totalled 35 patients, consisting of 19 women and 16 men. Table I records the essential data.

TABLE I.

Main diagnosis	*No. of cases*	*Average age*	*Clinical results*
Chronic brain syndrome	19	67	Nil
Parkinsonism.....	6	62	One much improved
Carcinoma and tumour	7	62	One much improved
Disseminated sclerosis..	3	50	Nil

The ages recorded in the table require a brief explanation. In the chronic brain syndrome group, the average age of 67 years does not altogether represent a true picture. This is accounted for by the inclusion of three young patients with hemiplegias. Actually, 15 of this first group of 19 patients were between the age of 62 and 86, the bulk falling into the middle and later seventies. The patients with parkinsonism also included one patient aged 49, whereas the remainder were between the ages of 64 and 68 years. The tumour group included two young patients with terminal carcinomatosis, aged 35 and 47. In such a small selection, a few younger patients will noticeably distort the statistics and reduce the average age of the group, and perhaps mislead the observer. It is difficult indeed to define those limits which could be universally accepted as the aged period of life. In this group reported, a small number of patients are included who can hardly be described as aged but who more truly present organic disturbances of the central nervous system with added affect disturbances. However, of the total patients, only five were under the age of 50, and 22 were over the age of 62, with a heavy weighting in the seventh and eighth decades. With these explanatory comments, this may more readily appear to justify the earlier description of them as an aged chronically ill group.

The diagnosis of chronic brain syndrome is a combined clinical-pathological diagnosis and includes cerebral arteriosclerosis, post-hemiplegic cerebral atrophy, hypertensive encephalopathy, senile cortical atrophy and cortical circulatory impairment from congestive failure. A number of patients presented multiple diagnoses, with the presence of diabetes, hip fracture, and cord bladder. Depression as an obvious clinical state was evidenced as a retarded inhibited state or appeared as the agitated form or the paranoid-depressed admixture. The drug appeared to have no effect on pain in those patients suffering from cancer. In some patients, when imipramine alone proved clinically ineffective, other drugs were added, but without any special value accruing because of the imipramine administration. The most consistent physical finding in the series was a slight fall in blood pressure. This has been noted by others. Toxic reactions included one patient with a rash, one with diarrhœa, one with severe epigastric distress, one with marked sweating and one with the development of marked agitation. Four patients in this group died during the trial of imipramine. These deaths were carefully reviewed and there was no association with the drug: three patients had terminal cancer deaths and one patient died of bronchopneumonia. Two patients in the series improved markedly. One of these patients had severe Parkinson's disease and a complicating agitated depression which had made her hospital care extremely difficult. A marked and sustained improvement took place after two weeks of imipramine therapy. The other patient had a cord tumour and paraplegia but without particular cerebral disease. He was acutely depressed, retarded and suicidal before imipramine therapy and improved markedly on the drug. Four other patients in the series seemed somewhat more tractable, but the improvement was too limited to be notable.

A note should be added about the four deaths. Close examination of the data supports our opinion that these deaths were unrelated to the administration of imipramine.

CASE 1.—S.C., a 35-year-old woman, was admitted on January 28, 1959, and died on April 22, 1959. A diagnosis of cancer of the cervix was made in September 1954, when she was treated with radium. In September 1958, a hysterectomy and an uretero-ileal transplant were performed. Later, a chordotomy was performed for severe pain. She was admitted for terminal care in January 1959 with a recto-vaginal fistula and widespread metastases. Gross infection of the neoplasm, pelvis, and recto-vaginal fistula, along with pyrexia, cachexia and severe anæmia, was present. Severe pain remained in spite of the chordotomy. The administration of imipramine was begun on February 16, 1959, and was continued for approximately seven

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weeks. Her course continued downhill and eventually ended in intestinal obstruction and terminal bronchopneumonia. Blood transfusions, opiates, and antibiotics were given. The post-mortem examination confirmed the diagnosis in every detail. (Imipramine was given here because no cerebral metastases were present and the patient was co-operative, rational and in marked distress.)

CASE 2.—M.G., a 59-year-old man, was admitted on February 19, 1959, and died on March 3, 1959. A bowel resection for cancer of the recto-sigmoid region was performed in 1953 and bowel obstruction developed in January 1959; laparotomy in November 1958 revealed widespread liver metastases. He became paraplegic from spinal metastases and this led to his present admission. As well, he was severely anæmic and cachectic, and had ascites. Pyrexia and pulmonary rales were present. His heart remained strong; control of pain was a problem. Imipramine administration was begun on February 26, 1959, and continued for two weeks. In addition the patient received antibiotics, oxygen, special nursing care, endotracheal aspirations, and opiates. His course continued steadily downhill. The final diagnosis was widespread carcinomatosis and terminal bilateral bronchopneumonia.

CASE 3.—S.P., a 55-year-old man, was admitted on February 26, 1959, and died on March 12, 1959. He had terminal carcinoma with pulmonary metastases, and finally pneumonia. Pain control was the problem, along with life-sustaining treatment.

CASE 4.—M.G., a 73-year-old man, was admitted on May 5, 1958, and died on February 12, 1959. He had cardiovascular disease and residual hemiplegia; blood pressure was usually about 220/120 mm. Hg. Depression, listlessness and negativism were present before imipramine administration. This drug was tried for four weeks with no resulting change other than a slight reduction in blood pressure. A gradual development of middle cerebral artery thrombosis began with the terminal pneumonia.

At the Hospital of Hope, the most common causes of demise are pneumonia, phlebitis with embolic phenomena, and cerebrovascular accidents. As already noted, it is our opinion that the administration of imipramine was not involved directly or indirectly in the expiration of the four patients.

DISCUSSION

Our clinical trial establishes that imipramine is ineffective in those patients in whom depression or the depressive equivalent reaction is complicated by marked organic cerebral deficit; this group of patients continues to present an unresolved therapeutic dilemma. This series confirms the finding that the drug is not particularly effective when other features are present to contaminate the depressed reaction. In a small group with severe and intractable pain, imipramine was not helpful. It remains to be seen whether milder pain states will be favourably influenced. Further, we can report, as a byproduct of this trial, that there is a considerable margin of safety in the use of this drug. Our group consisted entirely of severely ill, physically diseased and disabled persons; yet within the dosage limits indicated above, no formidable complications developed. One can assume that toxic reactions will more readily occur when dosages are employed that are beyond the usual therapeutic level. Apart from watchful caution, one need not restrict treatment with imipramine in those cases where its use is clinically indicated.

SUMMARY

Imipramine was clinically ineffective in a group of aged chronically ill hospital patients. This strengthens the original impression that its effectiveness diminishes with "contamination" of the purely depressed state. The main contaminant in the reported group was the presence of a gross cerebral organic deficit, the "chronic brain syndrome". Imipramine did not prove effective in the relief of severe pain in a small group of patients with carcinoma. It appears to be relatively nontoxic within dosage ranges acknowledged to be therapeutically effective.

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RÉSUMÉ

On a administré à un groupe de malades chroniques âgés, hospitalisés au *Jewish Hospital of Hope* de Montréal des doses habituelles d'imipramine. L'effet clinique qu'on espérait ne s'est pas manifesté. Cet échec confirme l'impression que l'efficacité de ce médicament diminue s'il y a "contamination" de la dépression pure par un déficit cérébral organique (le syndrome cérébral chronique des auteurs anglo-saxons). L'imipramine n'a pas contribué non plus au soulagement des grandes douleurs chez un petit nombre de cancéreux. Aux doses recommandées le médicament s'est avéré relativement inoffensif.

Case Reports

MEGALOBLASTIC ANÆMIA DUE TO ANTICONVULSANT THERAPY: REPORT OF A CASE RESPONDING TO VITAMIN B_{12}*

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IN THE PAST five years over 35 cases of megaloblastic anæmia associated with anticonvulsant drugs have been reported. To our knowledge only one of these occurred in North America. The vast majority have been related to therapy with diphenylhydantoin sodium (Dilantin), primidone (Mysoline) and barbiturates—singly or in combination. Most of these patients have responded to folic acid. A mechanism of impaired cellular metabolism of folic acid has been postulated. Only a few workers have reported cases responding to vitamin B_{12} alone.

The following case is presented in which a megaloblastic anæmia complicated by pancytopenia and secondary hæmorrhage occurred after long-term therapy with diphenylhydantoin sodium and phenobarbital. A vitamin B_{12} deficiency without dietary or absorptive defect was demonstrated. The anæmia responded to parenteral vitamin B_{12} therapy without the addition of folic acid.

A 45-year-old man was admitted to the Montreal General Hospital on April 6, 1959, with symptoms of abdominal pain and mental confusion of one week's duration. In 1934, epilepsy was diagnosed and treated with phenobarbital. Diphenylhydantoin sodium was added to this therapy in 1938. An electroencephalogram in 1949 showed a bilateral temporal abnormality compatible with a diagnosis of epilepsy. Mental dullness was noted. Anæmia was not present. Therapy was continued with phenobarbital 100 mg. daily and diphenylhydantoin sodium 300 mg. daily. From 1949 to 1959 the patient was not seen by a physician. He has not held regular employment since 1945 owing to mental dullness and frequent seizures. Seizures of minor type have occurred regularly from 1954 and recently have taken place daily. Pallor has been noted by his wife for some time. His diet has consisted of about two ounces of salt pork, fresh pork, beef or chicken daily, and as well, vegetable stews, soups, bread, cooked vegetables such as cabbage, and one glass of milk a day. Fresh fruits and vegetables have not been eaten. His condition seemed unchanged to his wife until one week before admission when he complained of abdominal cramps and diarrhœa and became confused, disorientated and hallucinated.

On admission the patient was disorientated, hallucinated and obese. The temperature was 101° F., blood pressure was 130/80 mm. Hg and respirations were 20/min. Hæmorrhages were present in both optic fundi. The large smooth pale tongue showed atrophy of the papillæ. Despite some brown pigmentation of the skin, extreme pallor of the mucous membranes and skin was present. Fine rales were heard at the lung bases and pedal œdema was recorded. No reflex or sensory changes were detected on neurological examination.

Laboratory studies on admission showed the hæmatocrit value to be 14%, red blood cell count 1,300,000/c.mm., Hb. level 4.6 g. per 100 ml., reticulocytes 1.1%, white cell count 1300/c.mm. with a normal differential count, and platelets 50,000/c.mm. The value of blood urea nitrogen was 12 mg. %, serum bilirubin 0.6 mg. %, serum phosphate 2.5 mEq./l., serum calcium 8 mEq./l. One week later the calcium level was 9 mEq./l. Serum albumin level was 3.0 g. % and globulin 1.9 g. %. Later the globulin level rose to normal. The bone marrow was megaloblastic and gastric analysis showed histamine-fast achlorhydria. Occult blood was not found in the stool. No growth resulted from blood cultures. The serum vitamin B_{12} level, before therapy, was determined to be 65 $\mu\mu$g./ml. using *Lactobacillus leishmanii* as the test organism. Normal values are usually over 200. Repeat gastric analysis including maximal histamine stimulation revealed no free acid. The result of the Schilling test, using 0.5 μg. of vitamin B_{12} tagged with cobalt 58, was a urinary excretion of 14 and 19% of the oral dose. This is considered to be within normal limits.[1] Fat absorption by the balance method was 90%. Radiograms of the chest and upper and lower gastrointestinal tract were normal. Sigmoidoscopy was negative, as was electrocardiography. The stools remained negative for occult blood except on the day of massive bleeding. No fish tapeworm segments or ova were recovered from the fæces.

After admission the patient was continued on diphenylhydantoin sodium 300 mg. and phenobarbital 100 mg. daily. Intramuscular vitamin B_{12} 100 μg. daily was started 24 hours from admission. After three days of treatment the reticulocyte count rose to 3%; the serum iron and unsaturated iron-binding capacity were 18 and 66 μg. % respectively. By the fourth day the white blood cell and platelet counts had not risen. The patient had a large hæmorrhage, several hundred millilitres of red blood being passed per rectum and oozing steadily from the mouth. No local cause for the bleeding was detected and, except for the low platelet count, results of coagulation tests were normal. Because of the continuing fever the patient was given penicillin, streptomycin and tetracycline. Two days later, on the sixth day, the platelet count fell to 18,000/c.mm.; the white blood cell count was still 2000/c.mm. Although the reticulocyte count had risen to 29% and the hæmatocrit value was rising, it was felt advisable to add prednisone 40 mg., ascorbic acid 600 mg., and vitamin K 20 mg. daily in the hope of evoking a platelet and W.B.C. response and to aid in hæmostasis. Phenobarbital was discontinued because of the possibility that it was contributing to the leukopenia and thrombocytopenia. However, diphenylhydantoin sodium was continued. By the eighth day the reticulocyte count reached a peak of 34%, the hæmatocrit rose to 19% and an increase in the white blood cell and platelet counts was noted. Prednisone was decreased and discontinued shortly afterwards along with ascorbic acid and vitamin K. Seizures

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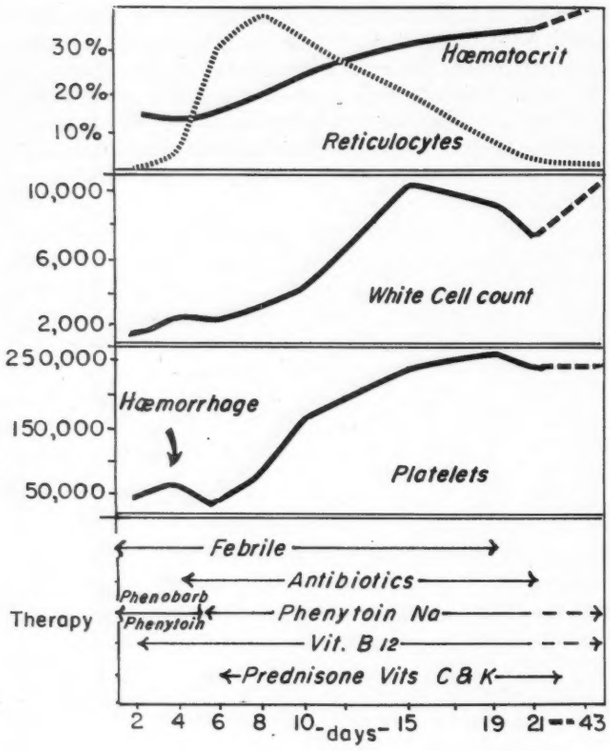

Fig. 1.

occurred up to the fifth day but not thereafter. At the end of the first week marked improvement was noted in the patient's mental state and appetite. All evidence of disorientation and hallucination had disappeared. On the 19th day the serum iron level and unsaturated iron binding capacity had risen to 67 and 102 μg. % respectively, although no iron had been administered. Fever disappeared at this time and antibiotics were discontinued. Progressive improvement continued until discharge 43 days after admission, at which time the hæmatocrit was 40%, W.B.C. count 8000/c.mm., platelet count 250,000/c.mm., serum vitamin B_{12} 381 μμg./ml., and bone marrow normoblastic. After discharge, he took 30 μg. of vitamin B_{12} weekly and diphenylhydantoin sodium 300 mg. daily. Three weeks after discharge the hæmatocrit was 45%. Because the previous Schilling tests had been performed while the patient was receiving diphenylhydantoin sodium only, he was given phenobarbital 100 mg. daily for one week and a third Schilling test was performed. A normal value was obtained, ruling out any possible effect of this drug on vitamin B_{12} absorption. Details of the course in hospital including therapy and laboratory determinations are shown graphically in Fig. 1.

DISCUSSION

In the past this patient would have been diagnosed as having pernicious anæmia. Tongue atrophy, severe macrocytic anæmia, megaloblastic bone marrow, histamine-fast achlorhydria and complete response to vitamin B_{12} would have been accepted as undisputed evidence. Even severe platelet deficiency inducing secondary hæmorrhage is known to occur in this disease[2] and leukopenia is not uncommon. However, three Schilling tests showed normal absorption of vitamin B_{12}, thus eliminating the diagnosis of pernicious anæmia by definition.

The megaloblastic anæmia, achlorhydria, low serum vitamin B_{12} level and normal Schilling tests could be all be explained by the patient's diet if it had been deficient in this factor. Pollycove,[3] reporting a substantiated case of dietary deficiency of vitamin B_{12}, points out that complete deprivation of dairy and meat products over a period of years is usually required to produce severe vitamin B_{12} depletion. Food assays[4, 5] would suggest that such a diet as that taken by our patient would contain a minimum vitamin B_{12} content of one to three micrograms daily, which is usually adequate to prevent deficiency. Although the folic acid content of the diet appeared limited, it was not grossly inadequate. Thus while the diet was probably borderline with respect to vitamin B_{12} and folic acid content, it cannot be considered the prime cause of the megaloblastic anæmia.

Impaired absorption of vitamin B_{12} such as occurs in the malabsorption syndrome and in the presence of fish tapeworm was disproved by the normal Schilling tests. The fat balance (90% absorption) was not markedly abnormal, nor were worm segments or ova recovered. However, a minimum folic acid absorptive defect is possible. No gross liver disease was demonstrated.

Thus, the clinical picture in our patient appeared to be related to the long-term anticonvulsant therapy. Although he received antibiotics, prednisone, ascorbic acid and vitamin K as well as parenteral vitamin B_{12}, the response is clearly due to the latter drug. A reticulocytosis of 3% and a very low serum iron value were noted by the third day of vitamin B_{12} therapy. Antibiotics were added. Two days later the reticulocyte count was 29%, which cannot reasonably be attributed to any antibiotic effect. The other drugs were begun after this maximum reticulocyte response. It seems probable that the achlorhydria was an incidental finding and unrelated to the problem of anæmia.

A review of the literature has revealed 39 other cases found acceptable by the following criteria: long-term anticonvulsant therapy, megaloblastic anæmia, the presence of free acid in the stomach or evidence of normal vitamin B_{12} absorption by radioactive techniques, the absence of steatorrhœa, pregnancy, fish tapeworm, liver disease, organic gastro-intestinal disease, and a definite response to liver, vitamin B_{12} or folic acid. Thirty-six cases fulfilled these criteria.[6-32] Three further cases were accepted: one patient did not have a bone marrow examination but the case was otherwise acceptable,[6] and two young girls, aged 19 and 21, with achlorhydria responded to vitamin B_{12}[6] (the likelihood of pernicious anæmia at this age seems remote). Some cases previously described have not been accepted, owing, in most instances, to the inability to exclude pernicious anæmia. In such circumstances radioactive vitamin B_{12} absorption

tests should always be done so that the distinction may be made. One further case was rejected because of pregnancy.[7]

These cases have occurred over a wide age-range, but the largest number have been reported in young adults. They have been associated with administration of diphenylhydantoin sodium (three cases); primidone (seven cases); and sodium secobarbital plus amobarbital (Tuinal) (one case), and the remainder with combinations of diphenylhydantoin sodium, primidone, and phenobarbital. Phenobarbital alone has not been implicated.

Gastric analysis was performed in all cases; only three were found to have no free hydrochloric acid after histamine stimulation.[6, 8, 9] Vitamin B_{12} absorption was studied by radioactive techniques in seven cases and found to be normal.[8, 10-14] Three subjects had normal folic acid absorption studies.[10, 11, 15] Serum vitamin B_{12} levels determined in 12 cases were low in two.[12, 16]

Folic acid produced complete remission in 12 patients. Ten responded well to folic acid after failure to respond to parenteral vitamin B_{12}. Five responded to combined therapy with vitamin B_{12} and folic acid or liver injections. However, in 12 patients vitamin B_{12} produced a complete response without other therapy. It is of interest that three patients had neurological symptoms: one, peripheral neuritis and two, subacute combined degeneration of the cord.[6, 17] All had normal gastric acidity and responded to vitamin B_{12}. Both patients with low serum vitamin B_{12} levels had normal gastric acidity but only one responded to vitamin B_{12}.[16] The other improved after receiving folic acid only.[12]

The effect of discontinuing anticonvulsant drug therapy is not known. Christenson[18] reported a case in which marked reticulocytosis took place after withdrawal of primidone. Hawkins[6] reports a decrease in macrocytosis in non-anæmic individuals on anticonvulsants some months after the drugs are stopped. On the other hand, Stokes and Fortune[19] and Gydell[20] have shown no effect after discontinuing therapy for eight days and four months respectively. In some cases the recorded response was possibly due to discontinuation of the anticonvulsant rather than to the hæmatinic. However, clinical responses to both folic acid and vitamin B_{12} therapy were complete among the 50% of the patients known to have continued anticonvulsant drugs.

Five years have passed since the first case of megaloblastic anæmia was described by Badenoch,[8] and although more than 35 cases have been recorded the exact mechanism producing this anæmia is not known. A number of facts have accumulated which permit certain speculations and some conclusions.

In several of the reported cases the diet was stated to be poor.[12, 17, 18] Rarely were details given. However, it can be surmised that since a number of these patients have been confined in mental institutions and others have undergone mental deterioration, the dietary intake of both folic acid and vitamin B_{12} may have been borderline. Possible cases of frank dietary deficiency have not been well documented. All evidence points to normal absorption of folic acid and vitamin B_{12} in this condition. Studies to determine depletion of folic acid stores were carried out by Chanarin[10] but no evidence of depletion was observed. The low serum levels of vitamin B_{12} noted in the occasional patient might be taken as evidence of tissue depletion.

As a result of these investigations, some authors have suggested that the defect is at the site of action of folic acid where a block of the competitive inhibition type may result from anticonvulsant therapy.[10, 17] The structural similarity of folic acid and the anticonvulsant drugs has been pointed out.[15] Although the vitamin B_{12} molecule does not resemble that of the anticonvulsant drugs, it has been suggested that the anticonvulsant drugs may interfere with its metabolism.[17]

It is of interest that the cases of Kidd,[12] Montgomery[16] and ourselves had low serum vitamin B_{12} levels. Montgomery's and ours responded to vitamin B_{12}; Kidd's case did not, and was treated with folic acid. The explanation of the low serum vitamin B_{12} is not clear. It may represent an altered metabolism of vitamin B_{12} or perhaps an increased requirement in the presence of folic acid deficiency. The fact that no patient failed to respond to folic acid, when it was tried, has been used to suggest that the defect is basically of folic acid metabolism. The therapeutic response of some patients to vitamin B_{12} may be due to the close interaction of folic acid and vitamin B_{12} in cell metabolism. Further, it has been suggested that vitamin B_{12} is only effective when at least some residual folic acid is available and that the vitamin B_{12} aids in its mobilization. However, there is no evidence that the metabolism of folic acid and vitamin B_{12} may not be disrupted together in some cases and singly in others.

It is possible that no single explanation will be found to permit an understanding of all these cases. Multiple factors may be involved. A diet may be relatively deficient in folic acid or vitamin B_{12} for the increased needs caused by the action of the anticonvulsant drugs. Supplemental folic acid and in many cases vitamin B_{12} will prevent recurrence of this type of anæmia. An adequate diet might do the same in some of these patients.

Fuld and Moorhouse have suggested the prophylactic use of folic acid in patients receiving anticonvulsant drugs.[21] This would appear hazardous as it would mask the development of pernicious anæmia and other vitamin B_{12} deficiency states. An acute awareness of this problem, with frequent hæmatological examination of patients receiving these drugs, and a thorough investigation of those found anæmic are essential.

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SUMMARY

A case of megaloblastic anæmia complicated by pancytopenia and secondary hæmorrhage occurring after long-term therapy with diphenylhydantoin sodium and phenobarbital is reported. Vitamin B_{12} deficiency without dietary or absorptive defect was demonstrated. The anæmia responded to parenteral vitamin B_{12} therapy without the addition of folic acid.

The literature of megaloblastic anæmia associated with anticonvulsant drug therapy is reviewed. Thirty-nine cases were found to be acceptable, only one of which was reported in the North American literature. Most of these patients responded to folic acid but a few obtained satisfactory remission on vitamin B_{12} therapy alone. On the basis of the information available from previously reported cases and the case presented here, the mechanism is discussed and certain suggestions as to etiology are put forward.

We wish to thank Drs. A. W. Lapin and D. Howell for permission to publish this case and Dr. S. R. Townsend for his assistance in the preparation of this paper.

ADDENDUM

Since the preparation of this paper a further case of drug-induced megaloblastic anæmia has been uncovered.[33] Phenyl-methyl barbituric acid was implicated. The patient responded to folic acid.

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MEGALOBLASTIC ANÆMIA ASSOCIATED WITH PHENOBARBITAL THERAPY*

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IN RECENT years a number of cases have been described[1-8] of megaloblastic anæmia associated with the administration of antiepileptic drugs. Most of these anæmias have responded to therapy with folic acid. The relative roles of the antiepileptic drugs and of dietary deficiency in the pathogenesis of these anæmias remain in doubt, but some association appears to exist between anæmias of this type and the administration of certain anticonvulsive agents.

The majority of such anæmias have been associated with the administration of diphenylhydantoin (Dilantin) or primidone, although scattered reports have also implicated other anticonvulsive drugs. In the case report presented below, phenobarbital was the sole anticonvulsive administered to the patient up to the beginning of his illness. Although megaloblastic anæmia has been described in patients treated with phenobarbital and another anticonvulsive agent, only one previous case has been reported[9] of megaloblastic anæmia associated with the administration of phenobarbital alone.

R.L., a 30-year-old white man and a French Canadian by descent, was admitted to the Royal Victoria Hospital on September 3, 1958. For the preceding three days he had been acutely ill with fever, repeated epileptic seizures, and progressive stupor.

The patient was severely mentally retarded and had never been gainfully employed. At five years of age he began to have major epileptic seizures and since that time had taken phenobarbital in doses up to 300 mg. daily. Details of his dietary history were impossible to obtain, but one could not exclude the possibility that his diet had consisted mainly of carbohydrate.

The present illness began two months before admission when his family noted that he was less active than usual. Subsequently he became anorexic, pale and weak, and lost weight. Ulcerations were noted on his gums, and seizures occurred with increased frequency. On July 30, one month before admission and one month after the onset of his illness, he was seen by his physician, who prescribed diphenylhydantoin 100 mg. twice daily in addition to the phenobarbital. The additional therapy had little effect on the seizures and he became increasingly weak and pale. Several days before admission he complained of fever and chills, and a discharge was noted from his left ear. Major convulsive seizures occurred frequently, and he was confined to bed. Only when he became too ill to resist, could hospitalization be arranged.

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On examination the patient was moderately well nourished and appeared to be his stated age. There was extreme pallor of the skin and mucous membranes; the patient was semi-stuporous and unco-operative when aroused. Generalized convulsive seizures lasting 1-2 minutes occurred every half hour, often several in succession. His temperature was 104.6° F. per rectum, pulse 130/min. and blood pressure 90/50 mm. Hg.

He was noted to be microcephalic and had a repaired hare lip. His pupils were large and reacted to light. Fundoscopic examination revealed well-outlined optic discs, engorged venules, and abundant scattered fresh irregular hæmorrhages bilaterally. A slight mucopurulent discharge was noted issuing from a perforation of the left eardrum. The right ear drum was bulging and later perforated, discharging pus. No mastoid tenderness was present.

His tongue was moist and coated, and the edentulous gums appeared normal, except for a few superficial ulcerations. A few slightly enlarged non-tender lymph nodes were present in the posterior triangles of the neck. No petechiæ or ecchymoses were seen on the skin or mucous membranes. The spleen was not palpable; no tenderness was present over the sternum. Rectal examination was normal and the stool was negative for occult blood. The seizures were of the major convulsive type without localizing features. Generalized muscle weakness was noted, although tone was normal. No neck stiffness was found. Neurological examination, including vibration sense, was normal. The remainder of the physical examination was unremarkable.

Urinalysis revealed one plus protein, and four to five red blood cells per high-power field in the centrifuged sediment. No red blood cells were noted on subsequent examinations.

The peripheral blood revealed the following values: Hb. 2.6 g. %; hæmatocrit 6%; R.B.C. 800,000/c.mm.; mean corpuscular volume 75 c.μ; mean corpuscular hæmoglobin 33 $\gamma\gamma$; mean corpuscular hæmoglobin concentration 43%; reticulocytes 0.5%; W.B.C. 1000/c.mm. The differential count showed: neutrophils (band) 30/c.mm.; neutrophils (mature) 510; monocytes 100; lymphocytes 360. The erythrocytes appeared normal in size and shape and were well filled with hæmoglobin; no macrocytes were seen. The clotting time was 11 min., bleeding time greater than 15 min., one-stage prothrombin time 18 sec. (normal 12½ sec.), prothrombic activity 27%. No platelets were seen on the smear. Prothrombin and proconvertin activity (determined by the method of Owren[10]) was 50%; prothrombin 66%; proconvertin 31%; Factor V 83%.

Bone marrow aspiration, performed on September 4, produced cellular smears; occasional megakaryocytes were present, but no platelet formation was seen. Erythroid maturation was markedly abnormal with severe megaloblastic changes at all stages of maturation. Myeloid activity was present with a relative paucity of mature neutrophils. Multilobed neutrophils, giant metamyelocytes and band forms were prominent. M:E ratio was 3:1. No tumour cells were seen. The impression was severe megaloblastic anæmia with large numbers of myeloid cells, most consistent with vitamin B_{12} or folic acid deficiency and with superimposed severe inflammation.

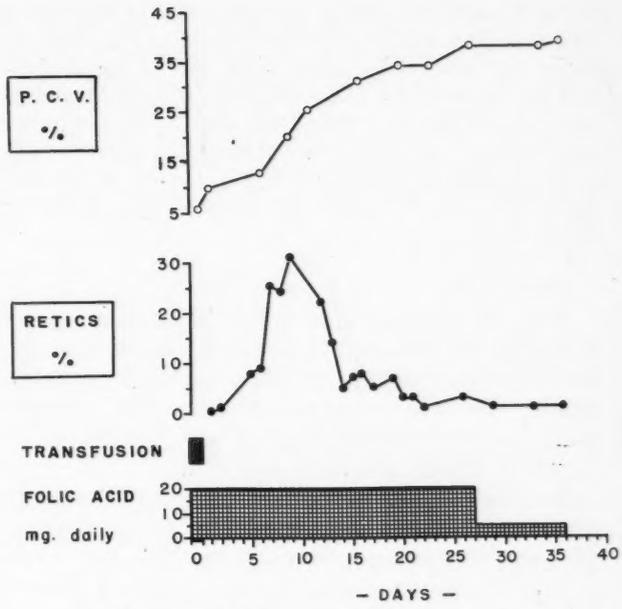

Fig. 1.—Case R.L. Response to folic acid.

Serum vitamin B_{12} level was assayed using *Lactobacillus leishmanii** and found to be 235 $\mu\mu$g./ml. (normal range over 150 $\mu\mu$g./ml.). Serum iron value was 185 μg. %; UIBC (unsaturated iron-binding capacity) 57 μg. %; and TIBC (total iron-binding capacity) 236 μg. %.

Free acid was present on gastric analysis. The result of a Schilling type of vitamin B_{12} absorption test, performed on October 10, was a urinary excretion of 20.8% of the administered radioactive vitamin B_{12} in 24 hours—normal range.

Biochemical studies, including liver function tests, non-protein nitrogen determination and serum electrophoresis, were normal, as was also a 72-hour fat balance study (6% of the stool was composed of fat). Radiological examination of the small bowel was normal.

The patient was diagnosed as having megaloblastic anæmia associated with anticonvulsive therapy and acute bilateral otitis media. For initial treatment, the patient received transfusions of 1000 ml. of whole blood and 250 ml. of packed red cells during the first 24 hours. After appropriate specimens for culture were taken, he was treated with tetracycline and sulfisoxazole. A high protein diet, 20 mg. of folic acid and 100 mg. of vitamin K were administered by mouth daily. Diphenylhydantoin was withdrawn but phenobarbital was continued, together with paraldehyde.

Clinically the patient became more responsive and improved in colour and strength. The otitis media subsided with antibiotic therapy. Hæmatological response is illustrated in Fig. 1. After two days of therapy with folic acid the reticulocyte count rose to 7.8% and the blood smear contained numerous polychromatophilic macrocytes. By the eighth day of this therapy, the reticulocyte count reached 31% and the Hb. level 6.0 g. %. The patient became afebrile on September 18 and no further sign of active ear disease existed. On September 24, in an effort to obtain better control

*Performed by Mr. E. Deschenes through the kindness of Messrs. Charles E. Frosst & Co.

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of the seizures, the patient was given diphenylhydantoin 100 mg. three times a day and phenobarbital 100 mg. every six hours. The subsequent rise in hæmoglobin was not impaired by this addition of Dilantin and there were no further seizures. Folic acid 5 mg. daily was administered as maintenance therapy. He was discharged feeling well on October 11, five weeks after admission. At that time the hæmoglobin level was 12 g. %.

DISCUSSION

This patient was found to have a severe folic acid deficiency. Although the possibility exists that this deficiency developed purely on the basis of dietary intake, the history obtained from the patient's family suggested that the diet was not devoid of vegetables, milk products and meat.

In view of the previously reported association of anticonvulsive therapy and folic acid deficiency, the possibility cannot be excluded that this severe folic acid deficiency was in some way conditioned by the administration of phenobarbital. The role of his severe infection in the pathogenesis of this deficiency cannot be accurately assessed.

Of 25 cases of megaloblastic anæmia associated with the administration of anticonvulsive drugs, described previously,[1-8] the majority were in epileptics suffering from major seizures who had received anticonvulsive therapy for several years before the development of the anæmia. The patients ranged in age from 17 to 52 years. Diphenylhydantoin (Dilantin) and phenobarbital were used singly or in combination in a total of 18 cases, primidone (Mysoline) was administered in seven, and secobarbital with amobarbital (Tuinal) was administered in one case.

These patients had severe anæmia with a megaloblastic bone marrow, and all had free acid present in the gastric secretions. Serum vitamin B_{12} levels were measured in nine of the cases, and six of these were within normal range. Two patients were shown to have abnormally low vitamin B_{12} levels but these were associated with poor dietary intake. The remaining serum vitamin B_{12} determinations revealed a low normal value. Vitamin B_{12} absorption was measured by means of the Schilling test in six patients and all showed normal excretion.

Four patients responded to vitamin B_{12} therapy alone and three others responded to a mixture of vitamin B_{12} and ascorbic acid. Ten patients showed an unsatisfactory response to vitamin B_{12} and subsequently responded to folic acid therapy. Seven patients were treated with folic acid alone with adequate therapeutic response. The one remaining patient was treated successfully by the complete withdrawal of anticonvulsive therapy. The results of therapy are difficult to assess, however, in view of the fact that in the majority of cases the suspected anticonvulsant was discontinued when the patient was admitted to hospital.

Chanarin *et al.*[6] studied the absorption and the plasma clearance of folic acid in a 44-year-old epileptic woman who developed a megaloblastic anæmia after receiving primidone for two years. They demonstrated that she absorbed folic acid normally from the gastro-intestinal tract, and that the clearance value of injected folic acid from her plasma was within the normal range. She responded to therapy with folic acid. In contrast, a group of patients with folic acid deficiency secondary to pregnancy or to the malabsorption syndrome were shown to have a more rapid plasma clearance of injected folic acid. These authors postulated that this patient had a normal tissue concentration of folic acid but that the utilization of the vitamin was blocked at a cellular level.

The critical problem in the evaluation of the importance of the anticonvulsive drugs in the pathogenesis of the megaloblastic anæmias has been the recognition of dietary deficiency of folic acid. Many of the cases reported above were of patients with severe epilepsy and mental changes. In such individuals an inadequate diet may be common. Despite the apparent similarity of the chemical structures of folic acid and of the anticonvulsants, the exact role of these agents in the pathogenesis of these megaloblastic anæmias is unknown. Further studies of absorption and utilization similar to those of Chanarin *et al.*[6] must be carried out, before the role of these drugs will be understood. One must accept the fact of an apparently increased incidence of megaloblastic anæmia in patients receiving anticonvulsive therapy.

The patient described here became ill after some years of phenobarbital therapy. The role played by his acute infection in precipitating the severe deficiency is unclear. The absence of a typical macrocytosis on blood smear on admission was also unusual. His dramatic hæmatological response was probably due to folic acid therapy, although it also coincided with successful antibiotic treatment of his infection.

SUMMARY

A case of severe megaloblastic anæmia in an epileptic who had been on prolonged phenobarbital therapy has been presented. Satisfactory remission of the anæmia followed administration of folic acid and antibiotic therapy for an acute infection, while at the same time administration of phenobarbital was continued. Twenty-five cases of megaloblastic anæmia reported in the literature associated with the administration of various anticonvulsive drugs have been discussed. The possible mechanisms of this anæmia are briefly reviewed.

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HYPOFIBRINOGENÆMIA FOLLOWING NORMAL PREGNANCY AND LABOUR

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AFIBRINOGENÆMIA or hypofibrinogenæmia complicating pregnancy is now a well-known condition. The majority of patients with this condition have what are considered to be antecedent pathological conditions. These include: septic abortion, missed abortion, toxæmia of pregnancy, premature separation of the placenta at term, amniotic fluid embolus, placenta prævia and intravenous administration of dextran.

The occurrence of hypofibrinogenæmia following a normal pregnancy and labour and giving rise to postpartum hæmorrhage is uncommon. A number of such cases have been described. Tagnon *et al.*[1] (1946) and Marchesi[2] (1954) described cases, both of which ended fatally. Kelsey and Muirhead[3] (1955) described a patient who survived after the use of fibrinogen, and of blood given intravenously and intra-arterially. Klein, Biskind and Silverberg[4] (1956) described a case which ended fatally.

The case to be presented is of a woman with an apparently normal pregnancy and labour.

A 24-year-old woman had had five previous pregnancies: three had terminated in abortion before 16 weeks; two had ended in premature labour at 32 and 36 weeks. Both premature infants survived. There was no history of hæmorrhage after any of these pregnancies.

The patient had had no serious past illnesses, and there was no history of abnormal bleeding.

The present pregnancy had been uneventful. Four weeks before delivery the blood pressure rose to 130/90 mm. Hg. Five days later, it settled to its previous level of 110/70 and remained there; no albuminuria. Total weight gain was 26 lb. No hæmorrhage and no abdominal pains developed.

Labour commenced spontaneously seven days after the expected date of delivery. The first stage was uneventful; no sedation was necessary. The second stage was short. When the fetal head was on the perineum a low forceps delivery was performed under ether anæsthesia. A live male infant weighing 7 lb. 7 oz. was delivered. The placenta was expressed completely a few minutes later. Ergometrine, 0.2 mg., was given intramuscularly immediately after delivery of the placenta. The total duration of labour was four and a half hours.

After the third stage a slight but steady loss of blood persisted per vaginam. The loss was unaffected by massaging the fundus uteri, and by the further administration of ergometrine.

Thirty minutes after completion of the third stage, it was decided that the cervix be examined. Examination was performed under general anæsthesia. Bleeding was seen to be coming from the uterus. The uterus was then packed. After a few minutes, blood was seen coming through the pack. Intravenous dextran had already been started while the uterus was being packed.

Three hours from completion of the third stage the blood pressure had fallen to 60 mm. Hg systolic; the diastolic pressure could not be obtained. Bleeding continued at the same steady rate; 500 c.c. dextran had been given intravenously.

Blood was substituted for the dextran. A second bottle of blood was begun through a cut-down in the right leg. During the next hour 1500 c.c. blood, 500 c.c. dextran, and 1000 c.c. saline were given intravenously. The blood pressure rose to 110/80. Bleeding continued. At this point, blood was withdrawn in order to estimate the fibrinogen level. It was estimated to be 80 mg. % (normal value 200-400 mg. %).

Two grams of fibrinogen were given intravenously. Blood loss through the pack stopped almost immediately.

The blood transfusions were continued until six hours after delivery. Altogether four and a half litres of citrated blood were given. Calcium gluconate was also given intravenously to the amount of 10 c.c. for every litre of blood.

The patient did not bleed further. Her blood pressure at the end of the transfusion was 120/80. A catheter was inserted into the bladder and left in until the uterine pack was removed 48 hours after delivery. Tetracycline was given orally for nine days.

Fourteen days after delivery the patient developed a staphylococcal septicæmia which probably arose from the cut-down site on her right leg. This eventually responded to chemotherapy.

SUMMARY

This patient had a normal pregnancy and labour, followed by a postpartum hæmorrhage. The bleeding was not heavy at any time. It was however persistent, so that the total loss was estimated at approximately five litres. The diagnosis of hypofibrinogenæmia was not made until three hours after delivery. At that time the level was only 80 mg. %, well below the normal range of 200 to 400 mg. %. The response to intravenous fibrinogen was instantaneous.

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MYELOGRAPHY AND BRACHIAL PLEXUS INJURIES

In the January 1960 issue of the *Canadian Journal of Surgery* (3: 113, 1960) Héon and Sirois discuss the value of the myelogram as a diagnostic and prognostic aid in traumatic lesions of the brachial plexus. They point out that traction injuries of the upper part of the brachial plexus are common enough to be encountered by most practitioners, and present both diagnostic and therapeutic problems. Although clinical indications help in diagnosis, they do not differentiate root tears within and outside the spinal cord. They describe three cases in which myelography was helpful. Nevertheless, although myelography is helpful in estimating prognosis, it is not an infallible guide to reversibility of the lesions.

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Special Article

CIGARETTE SMOKING AND LUNG CANCER IN CANADA*

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A GREAT MANY studies carried out in eight different countries have shown an extremely high degree of association between cigarette smoking and lung cancer. This relationship appears to be largely confined to epidermoid and undifferentiated bronchogenic carcinoma which are by far the commonest types of lung cancer in man. The epidemiological evidence together with evidence from pathological and experimental studies is sufficient to have convinced the British Medical Research Council[1] that cigarette smoking is a major cause of lung cancer. Most students of the subject, including the present authors, concur in this conclusion.[2]

No one claims that cigarette smoking is the only cause of lung cancer. For example, it appears to be well established that long exposure to heavy concentrations of dust containing uranium, chromates, or nickel carbonyl[3] produces a high incidence of lung cancer and there is evidence of a somewhat higher incidence of lung cancer among painters, hot metal workers, and a few other occupation groups.[4, 5] Furthermore, there is suggestive evidence that general air pollution in some cities[6] may be a factor in the occurrence of lung cancer in those areas. In our opinion, the case against general air pollution as a cause of lung cancer is not yet well established. In any event, in most areas it appears to be of minor importance compared with cigarette smoking and probably of less importance than occupational exposures of certain types. Nevertheless, it is possible that in some few industrial areas the general population is exposed to specific types of fumes or dusts to such a degree as to create a lung cancer hazard.

Our present concern is to obtain better estimates of the proportion of lung cancer which can be attributed to cigarette smoking in various parts of the world an in various socio-economic classes. That which cannot be attributed to cigarette smoking must be due to some other factor or combination of factors. It is hoped that studies of geographic and socio-economic variations in this respect will give leads for further research on the causes of lung cancer. This study is concerned with cigarette smoking and lung cancer in Canada as compared with other countries.

As Doll[7] and his associates have pointed out, there is a fairly high degree of correlation between age standardized lung cancer death rates in various countries and the per capita consumption of cigarettes in those countries several decades ago. However, there are a few exceptions. For example,

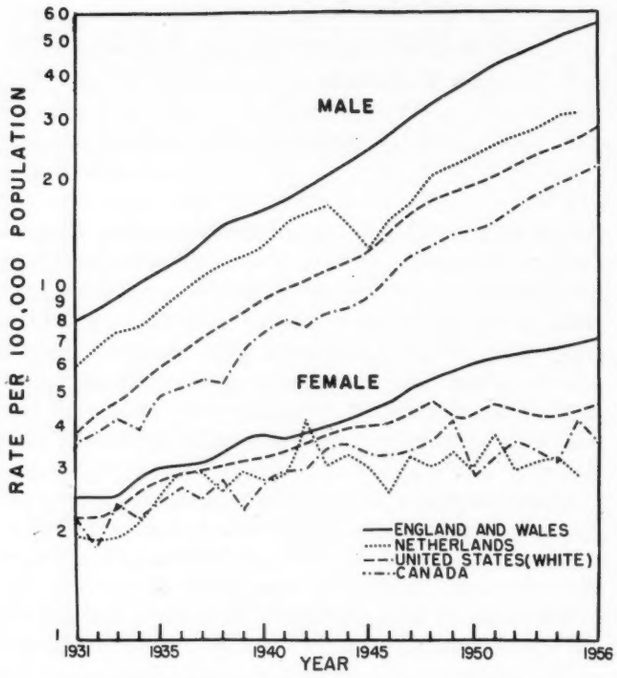

Fig. 1.—Death rates for cancer of the lung* by sex—four countries, 1931-1956.

*Standardized for age on the 1940 census population of the U.S.
Source of data: United States National Office of Vital Statistics; Netherlands Centraal Bureau voor de statistiek; England and Wales Registrar General; Canada Dominion Bureau of Statistics.

the United States and Japan have lower lung cancer death rates among men while the Netherlands, Austria, and England and Wales have higher lung cancer death rates among men than one might have predicted from considering only the per capita sale of manufactured cigarettes in these countries in 1930. The lung cancer death rate of males in Canada is very slightly lower than what might have been predicted from per capita cigarette consumption in 1930.

Fig. 1 gives lung cancer death rates (standardized for age by the direct method) for males and females in Canada, the United Kingdom, and the Netherlands, and for white males and females in the United States from 1931 to 1956. Fig. 2 indicates the consumption of manufactured cigarettes per adult in these countries from 1920 to 1956. The United Kingdom and the Netherlands were selected for this illustration because lung cancer death rates in these countries are much higher than might have been predicted from cigarette sales in prior years and the United States was selected because the lung cancer death rates are lower than might have been predicted from cigarette sales. It should be noted that in most countries a change was made in 1948 in procedure for reporting death rates by cause of death. Therefore, rates reported for years prior to 1948 are not strictly comparable to rates reported for later years.

Lung cancer death rates apparently vary in different socio-economic classes as well as in different countries. Cohart[8] has reported that the incidence rate of lung cancer in New Haven, Connecticut, U.S.A., is about 40% greater among the poor than among the richer classes. This is in

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agreement with findings of Nielsen and Clemmensen[9] in Denmark. Dorn and Cutler,[10] studying ten metropolitan areas in the United States, found a remarkably consistent increase in the incidence rates of lung cancer with decreasing socio-economic class as indicated by income.

Sackrin and Conover[11] made a study of smoking habits of persons in the U.S.A. in relation to age and income. When adjusted for age, the data indicated that the proportion of males who smoke cigarettes regularly increases slightly with income levels, rising from $1000 per year up to about $5000 per year, and then decreases, proportionately fewer cigarette smokers being in the richest groups than in the poorest groups.

At least in the United States and in England and Wales, women over the age of 60 smoke far less than men. For example, in England and Wales[12] the proportion of people who smoke cigarettes in age-group 60 and over is reported to be 52.6% for men and 28.8% for women. In the United States[13] in age-group 65 and older, it is reported that about 28.8% of men and only 8.1% of women smoke cigarettes. In both countries women who smoke tend to smoke fewer cigarettes per day than do men who smoke cigarettes. Few women over the age of 60 smoke as many as 20 cigarettes per day.

We have been unable to find data of this kind for Canada.

Exposure to Cigarette Smoke

The average consumption of cigarettes per adult gives only a crude estimate of the exposure of a population to cigarette smoke. For adequate comparisons, we would at least need to know the consumption of cigarettes by sex and by age-groups during the last few decades in each area under consideration. Unfortunately, these data are not available. Aside from this, the number of cigarettes consumed by an individual is far from a perfect measure of his exposure to cigarette smoke products.[14] Other variables include: (1) the degree to which the individual inhales the smoke; (2) the type of cigarette including length, tobacco mixture, presence or absence of filter, and effectiveness of the filter if present; and (3) the proportion of each cigarette consumed.

There is evidence that the proportion of cigarette smokers who inhale the smoke is about the same for the United Kingdom as for the United States.[15] Evidence on this is lacking in other countries.

The factor of most interest to us in this report is the proportion of each cigarette consumed. Some years ago it was suggested that the typical smoker in the United Kingdom and in the Netherlands tends to smoke as much as possible of each cigarette while more wasteful Americans tend to discard their cigarettes when the butt is still quite long. This impression has recently been confirmed by studies of cigarette butts discarded by smokers in these three countries.[7, 16, 17] For reasons which will be discussed later, this difference in smoking habits may at least partially account for the reported differences in lung cancer death rates in these three countries.

Following this lead, we decided to make studies of cigarette butt lengths in various countries throughout the world. We started in Canada and our findings are reported in this paper.

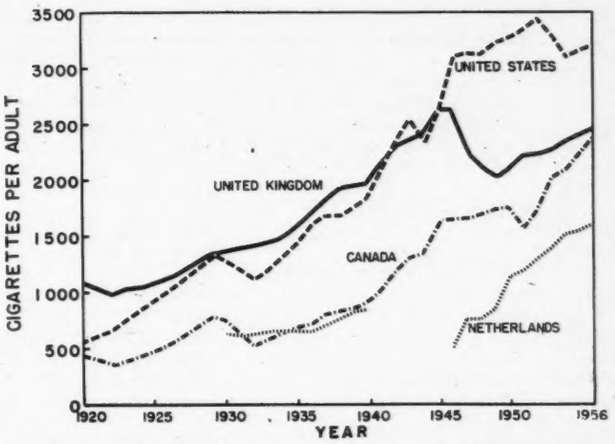

Fig. 2.—Consumption of cigarettes per adult—Canada, United States, United Kingdom and the Netherlands—1920-1956. Note: Figures not available for Netherlands before 1930 and 1940-45. Source: Tobacco Manufacturers' Standing Committee, Research Paper No. 1, Statistics of Smoking, 6-10, Bruton Street, London, W.1. 1957.

Method

In January and February 1959, 6428 discarded cigarette butts were collected in Montreal, Toronto, Vancouver, and Hamilton. They were obtained from many different locations including private homes, restaurants, business offices, factories, city streets, washrooms of department stores, railway stations, bus terminals and airports. In order to determine whether socio-economic class was a factor of importance, collections were made in upper-class, middle-class, and lower-class neighbourhoods in each of the four cities.

After collection, the butts were sorted by brand and by presence or absence of lipstick marks. The total length of the paper remaining on each butt was then measured in millimetres. In cases where the cigarette burned down farther on one side than on another side, the average length of the remaining paper was recorded.

Findings

Table I gives a general summary of the findings. A total of 6428 cigarette butts was collected. The mean length was 27.9 mm. Only 1.8% were under 15 mm. in length; 12.9% were 15 to 19 mm.; 65.2%, 20 to 34 mm.; 9.7%, 35 to 39 mm.; 5.8%, 40 to 44 mm., and 4.6% were 45 mm. or longer. Of the 6428 butts, 3535 (55%) had filter-tips and 2893 (45%) did not have filter-tips. The filter-tip butts averaged 28.3 mm. in length and the non-filter-tip butts averaged 27.3 mm.

Butts with lipstick marks were presumed to have been smoked by females, while most (though not all) of those without lipstick marks were, presumably, smoked by males. Classified in this way, 798 butts were smoked by females and most of the remaining 5630 presumably by males. Those smoked by females averaged 28.5 mm. in length and those by males averaged 27.8 mm.—a difference of 0.7 mm. This difference, though small, is statistically significant ($P = .008$).

Of the 798 butts smoked by females, 447 (56.0%) had filter-tips and 351 (44.0%) did not have filter-

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TABLE I.

MEAN LENGTH OF CIGARETTE BUTTS IN MILLIMETRES AND PERCENTAGE DISTRIBUTION OF LENGTHS OF BUTTS BY TYPE OF CIGARETTE, SEX, LOCATION, AND SOCIO-ECONOMIC CLASS

Location, socio-economic class, type of cigarette, and sex	*No. of butts*	*Mean length in mm.*	*Length of butts in mm.*									
			<15 %	*15–19* %	*20–24* %	*25–29* %	*30–34* %	*35–39* %	*40–44* %	*45–49* %	*50–54* %	*55–59* %
Total	6428	27.9 ± .11	1.8	12.9	22.9	24.0	18.3	9.7	5.8	2.4	1.3	0.9
(a) Type of cigarette												
Non-filter-tip	2893	27.3 ± .16	3.1	12.4	24.5	24.5	17.3	8.4	5.5	2.2	1.2	0.9
Filter-tip	3535	28.3 ± .15	0.7	13.3	21.6	23.4	19.1	10.8	6.0	2.6	1.4	1.1
(b) Sex and type of cigarette*												
Male—total	5630	27.8 ± .11	1.9	12.9	23.2	24.0	18.0	9.8	5.5	2.5	1.2	0.9
Male—non-filter-tip	2542	27.2 ± .17	3.4	12.2	25.4	24.6	16.8	8.2	5.2	2.2	1.3	0.9
Male—filter-tip	3088	28.3 ± .13	0.7	13.4	21.4	23.6	19.0	11.1	5.8	2.8	1.2	1.0
Female—total	798	28.5 ± .24	0.9	13.0	20.4	23.4	20.4	9.4	7.4	2.1	1.6	1.3
Female—non-filter-tip	351	28.5 ± .37	1.4	13.7	17.9	23.9	21.4	9.7	7.7	2.8	0.6	0.9
Female—filter-tip	447	28.4 ± .34	0.4	12.5	22.4	23.0	19.7	9.2	7.2	1.6	2.5	1.6
(c) Location												
Homes (houses)	907	27.7 ± .28	1.5	13.5	21.3	27.2	17.6	10.3	4.7	1.7	1.4	0.8
Homes (apartments)	707	27.8 ± .32	1.8	12.3	25.8	23.2	17.3	10.5	5.2	2.7	0.4	0.8
Restaurants	955	27.8 ± .26	1.3	11.5	22.6	26.6	20.8	8.8	4.6	2.0	1.4	0.4
Streets	675	28.6 ± .26	0.7	11.0	20.4	23.7	19.7	12.6	7.7	2.7	1.2	0.3
University students	419	26.9 ± .33	1.9	15.3	25.5	24.1	15.0	9.1	5.0	2.4	1.2	0.5
Washrooms in department stores	391	29.5 ± .47	1.3	12.5	14.8	25.4	20.3	9.7	10.7	2.3	1.0	2.0
Railway stations, bus depots, airports	411	28.4 ± .48	1.2	12.4	28.1	16.3	20.0	7.3	7.1	3.2	2.7	1.7
Place of work	1963	27.6 ± .21	2.6	13.8	23.4	22.9	17.3	9.3	5.2	2.8	1.3	1.4
(d) Socio-economic class												
Upper class	1554	31.4 ± .23	0.8	6.2	14.6	21.7	23.9	15.6	8.8	4.2	2.5	1.7
Middle class	1510	27.8 ± .22	1.3	12.0	24.6	25.0	17.5	9.7	5.9	2.1	1.1	0.9
Lower class	1735	25.5 ± .18	2.8	16.3	28.5	26.3	14.9	6.3	2.7	1.5	0.5	0.3

*Butts with lipstick marks were assumed to have been smoked by females. All others were assumed to have been smoked by males although some of these were probably smoked by females.

tips; while of the 5630 butts presumably smoked by males 3088 (54.8%) had filter-tips and 2542 (45.2%) did not have filter-tips. This small difference between the sexes in respect to type of cigarette smoked is not statistically significant. Non-filter-tip butts discarded by men were somewhat shorter on the average than those discarded by women, but the difference is not statistically significant. There was almost no difference in lengths for non-filter butts smoked by men and women.

The location of the smoker seems to make some difference in the length of the discarded butts. The longest, on the average; were those collected in washrooms of department stores and the next longest were those collected from streets and from railway, airport, and bus depots. Those collected in private homes, in apartment homes, and in places of work (e.g., offices, factories) were about the same average length.

Homes, restaurants, streets, and places of work were divided up according to apparent socio-economic class. Butts from the upper class averaged 31.4 mm. in length; those from the middle class averaged 27.8 mm., and those from the lower class averaged 25.5 mm. The differences of 5.9 mm. in average length between butts from the upper class and butts from the lower class is statistically significant ($P < 0.00001$). Butts collected from university students averaged 26.9 mm., which is intermediate between the average length of those collected from the middle class and the average length of those collected from the lower class. Butts collected from washrooms of department stores and from depots were not classified by socio-economic class since persons of all classes congregate in such places.

It should be noted that segregation of butts according to socio-economic class of the smoker was far from perfect. For example, some neighbourhoods are inhabited predominantly (but not exclusively) by persons of the upper socio-economic class and others are inhabited predominantly (but not exclusively) by persons of the lower socio-economic class. Thus, there is reason to suppose that some of the butts collected in a particular area had been discarded by persons of a different socio-economic class from that of the predominant population of that area. Overlapping of categories usually results in an under-estimate of the true difference between categories. Therefore, it is likely that the actual difference between socio-economic classes in respect to average length of cigarette butts is somewhat greater than the figures just quoted appear to indicate.

During the last several years, filter-tip cigarettes have become increasingly popular in comparison with non-filter ones. Socio-economic class seems to be of some importance in this respect. The percentages of filter-tip butts collected in this study was 59.4% for the upper class, 61.3% for the middle class, and only 44.4% for the lower class. Of 399 butts collected from professional people (e.g., doctors, lawyers) 64.2% had filter-tips.

Table II indicates the average length of cigarette butts by location, by type of cigarette, and by socio-economic class. It will be noted that for filter-tip cigarettes as well as for non-filter-tips and for every location, the average length of the butts was greater for the upper than for the lower class. Furthermore, in 11 out of 12 comparisons the average length of the butts was greater for the middle class than for the lower class; and in 10 out of 10 comparisons the average length of the butts was greater for the upper class than for the middle class. This consistency is a good indication that the observed differences in butt lengths by socio-economic classes is a correct finding and not merely the result of possible bias in sampling.

From the standpoint of exposure, what matters is not so much the length of the butt but the

TABLE II.
MEAN LENGTH OF CIGARETTE BUTTS IN MILLIMETRES BY LOCATION, TYPE OF CIGARETTE, AND SOCIO-ECONOMIC CLASS

Location:	Non-filter-tip			Filter-tip			Total			
	Upper class	*Middle class*	*Lower class*	*Upper class*	*Middle class*	*Lower class*	*Upper class*	*middle class*	*Lower class*	*Grand total*
Total with class specification	30.6 ± 0.37	28.3 ± 0.36	25.3 ± 0.24	31.9 ± 0.29	27.4 ± 0.27	25.8 ± 0.30	31.4 ± 0.23	27.8 ± 0.22	25.5 ± 0.18	28.1 ± 0.13
Homes (houses)	30.1 ± 0.84	28.3 ± 0.86	24.8 ± 0.48	31.7 ± 0.64	27.7 ± 0.63	23.9 ± 0.55	31.1 ± 0.51	27.9 ± 0.51	24.4 ± 0.36	27.7 ± 0.28
Homes (apartments)	29.3 ± 0.80	27.8 ± 1.37	25.7 ± 0.68	30.6 ± 0.86	26.8 ± 0.57	24.8 ± 0.61	29.9 ± 0.54	27.0 ± 0.55	25.2 ± 0.46	27.8 ± 0.32
Restaurants	31.5 ± 0.82	27.7 ± 0.64	25.9 ± 0.50	30.8 ± 0.53	27.0 ± 0.59	24.8 ± 0.72	31.0 ± 0.45	27.2 ± 0.47	25.5 ± 0.38	27.8 ± 0.26
Streets	31.0 ± 0.88	29.5 ± 1.02	27.3 ± 0.60	30.7 ± 0.79	27.2 ± 0.70	27.4 ± 0.73	30.8 ± 0.59	28.0 ± 0.58	27.3 ± 0.48	28.6 ± 0.26
Other specified location	— —	27.6 ± 0.94	23.3 ± 0.83	— —	29.4 ± 1.02	26.5 ± 1.12	— —	28.5 ± 0.69	24.6 ± 0.68	26.6 ± 0.50
Places of work:										
Professional workers	31.5 ± 0.78	— —	— —	34.3 ± 0.59	— —	— —	33.3 ± 0.46	— —	— —	33.3 ± 0.46
White collar workers	— —	28.9 ± 0.66	— —	— —	27.2 ± 0.59	— —	— —	27.9 ± 0.44	— —	27.9 ± 0.44
Industrial workers	— —	— —	24.9 ± 0.50	— —	— —	27.0 ± 0.60	— —	— —	25.9 ± 0.39	25.9 ± 0.39

amount of the cigarette which was consumed by the smoker. A maximum estimate of this can be obtained by subtracting the length of the discarded butt from the original length of the cigarette. (We say "maximum estimate" because some of the cigarette may have burned while not in the mouth of the smoker.) In order to make these estimates, it is necessary to know the original length of the cigarette. This can be determined when it is possible to identify the brand of the cigarette from the butt. The band was successfully identified for 2619 (74%) of the 3535 filter-tip butts. In most instances, where brand could not be identified, the reason was that so much of the cigarette was smoked that the brand name was burned off. Thus, the average length of the butts of unidentified brands (and unidentified original lengths) was considerably less than the average length of butts of identified brands. This must be taken into consideration when studying the figures presented in Table III. Only 1018 (35%) of the non-filter-tip butts could be identified as to brand. The brand name is usually printed near one end of non-filter cigarettes. Thus, the brand cannot be identified: (1) if the smoker lights the end bearing the name, or (2) if the smoker lights the other end but consumes a large proportion of the cigarette.

Table III shows the average lengths of the butts and the average consumed lengths in relation to type of cigarette, original length of cigarette, and socio-economic class. Most filter-tip cigarettes sold in Canada are of one of three lengths: 72 mm., 74 mm., or 80 mm. In most of the 72 mm. filter-tip cigarettes, the filter measures 11 mm.; and in most of the 74 mm. filter-tip cigarettes, the filter measures 13 mm. In the most popular brands of 80 mm. filter-tip cigarettes, the filter measures 15 mm. and in most other brands of this length, the filter measures 13 mm. The average original length of the filter-tip cigarettes in this study was approximately 75.7 mm. and the average length of the butts was 28.3 mm. Thus, on the average, about 47.4 mm. of filter-tip cigarettes was consumed. This is 62.6% of the average over-all length of 75.8% of the tobacco portion of the cigarettes.

It is curious that the average length of the butts of 80 mm. filter-tip cigarettes was somewhat less than the average length of the butts of the 72 mm. and 74 mm. filter-tip cigarettes. Conceivably, this might be an artifact resulting from the position of the name on cigarettes of various brands (this having a bearing on the ability to identify the brand name of very short butts). Be this as it may, there is certainly no indication that smokers of long cigarettes tend to discard a longer butt than do smokers of short cigarettes. The longer the cigarette, the greater is the length of tobacco consumed. This was found to be true in all three socio-economic classes.

Most non-filter cigarettes sold in Canada are either 72 mm. or 74 mm. in length although some are 70 mm. and some are as long as 85 mm. The average original length must be close to 73 mm. and the average length of the butts was 27.3 mm. Thus, on the average, about 45.7 mm. of non-filter-tip cigarettes is consumed, this being 62.6% of the original length. It appears that smokers of 74 mm.

TABLE III.
MEAN LENGTH OF CIGARETTE BUTTS IN MILLIMETRES AND MEAN LENGTH OF CIGARETTE CONSUMED BY TYPE AND LENGTH OF CIGARETTES

Type and length of cigarettes	*Total*			*Upper class*		*Middle class*		*Lower class*		*Class not specified*	
	No. of butts	*Mean length of butts*	*Mean length consumed*	*Mean length of butts*	*Mean length consumed*	*Mean length of butts*	*Mean length consumed*	*Mean length of butts*	*Mean length consumed*	*Mean length of butts*	*Mean length consumed*
Total (75.0 mm. mean)	6428	27.9 ± 0.11	47.1	31.4 ± 0.23	43.6	27.8 ± 0.22	47.2	25.5 ± 0.18	49.5	27.2 ± 0.22	47.8
Filter-tip (75.7 mm. mean)	3535	28.3 ± 0.15	47.4	31.9 ± 0.29	43.8	27.4 ± 0.27	48.3	25.8 ± 0.30	49.9	27.9 ± 0.29	47.8
72 mm.	341	31.6 ± 0.41	40.4	33.7 ± 0.75	38.3	30.2 ± 0.91	41.8	30.7 ± 0.74	41.3	31.6 ± 0.87	40.4
74 mm.	1432	31.2 ± 0.22	42.8	33.7 ± 0.40	40.3	30.1 ± 0.43	43.9	29.1 ± 0.46	44.9	31.0 ± 0.42	43.0
80 mm.	806	30.4 ± 0.28	49.6	33.2 ± 0.50	46.8	29.3 ± 0.50	50.7	27.3 ± 0.58	52.7	30.6 ± 0.61	49.4
Other* (82.4 mm. mean)	40	35.6 ± 1.22	46.8	37.2***	45.2	34.4***	48.0	36.7***	45.7	33.8***	48.6
Unknown length**	916	20.5 ± 0.18	—	22.6 ± 0.61	—	20.7 ± 0.30	—	19.7 ± 0.27	—	19.9 ± 0.31	—
Non-filter-tip (73.0 mm. mean)	2893	27.3 ± 0.16	45.7	30.6 ± 0.37	42.4	28.3 ± 0.36	44.7	25.3 ± 0.24	47.7	26.3 ± 0.33	46.7
70 mm.	80	28.3 ± 0.89	41.7	30.8***	39.2	28.2***	41.8	28.9***	41.1	26.1***	43.9
72 mm.	443	30.2 ± 0.46	41.8	32.9 ± 0.98	39.1	31.3 ± 0.89	40.7	26.7 ± 0.68	45.3	30.8 ± 1.09	41.2
74 mm.	470	28.6 ± 0.39	45.4	31.7 ± 0.86	42.3	29.7 ± 0.89	44.3	26.3 ± 0.44	47.7	27.6 ± 0.85	46.4
Other* (81.4 mm. mean)	25	34.4 ± 2.17	47.0	31.2***	50.2	32.3***	49.1	30.1***	51.3	42.3***	39.1
Unknown length**	1875	26.2 ± 0.19	—	29.5 ± 0.45	—	27.2 ± 0.43	—	24.6 ± 0.28	—	24.9 ± 0.35	—

*"Other" includes rare brands of unusual lengths and some brands which are sold in two or more different lengths and cannot be distinguished by the butts.
**"Unknown length" refers to butts of unidentifiable brands; this was usually because the name was burned off.
***Less than 25 butts; means very unstable statistically.
NOTE: The mean lengths indicated for totals is based upon the assumption that the distribution of original cigarette lengths of unidentified brands was the same as the distribution of lengths of identified brands.

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non-filter-tip cigarettes consume more tobacco per cigarette than do smokers of 70 mm. or 72 mm. non-filter cigarettes. This was the case in all three socio-economic classes.

The cigarette butts were collected in four cities. The percentage with filter-tips was 57.2% in Montreal, 57.1% in Toronto, 52.2% in Vancouver and 52.7% in Hamilton. The average lengths of the butts was 30.4 mm. in Montreal, 27.2 mm. in Toronto, 27.3 mm. in Vancouver, and 25.5 mm. in Hamilton. In all four cities: (1) the average length of the filter-tip butts was greater than the average length of the non-filter-tip butts, and (2) the average length of the butts was greatest for the upper class and least for the lower class. The low average length of the butts collected from Hamilton is partly accounted for by the fact that the proportion of butts collected from the lower classes was greater in Hamilton than in any of the other three cities.

TABLE IV.
COMPARISON OF CIGARETTE BUTTS COLLECTED IN THE U.S.A., CANADA, THE NETHERLANDS, AND ENGLAND AND WALES

Length of butt (mm.)	*U.S.A.*[16] %		*Canada** %		*Netherlands*[17] %		*England*[7] *and Wales* %	
< 10		0.8	0.1	1.8	1.8	15.6	1.2	18.7
10-14			1.7		13.8		17.5	
15-19	7.9		12.9		32.4		46.7	
20-24	19.7		22.9		28.7		25.4	
25-29	19.9		24.0		13.0		6.9	
30-34	20.9		18.3		5.3		1.4	
35-39	12.8	51.7	9.7	38.4	2.9	10.3	0.6	2.3
40 +	18.0		10.4		2.1		0.3	
Total butts measured	4283 (100%)		6428 (100%)		890 (100%)		772 (100%)	
Mean length (mm.)	30.9		27.9		20.8		18.7	
Mean length (mm.):								
Males.....	—		27.8		—		19.3	
Females...	—		28.5		—		17.3	
Upper class	—		31.4		—		—	
Middle class	—		27.8		—		—	
Lower class	—		25.5		—		—	

*Present study.

DISCUSSION

Table IV gives a comparison of the lengths of cigarette butts collected in Canada, the United States, the Netherlands, and England and Wales.

Hammond[16] in the United States and Korteweg[17] in the Netherlands used the same method of collecting butts as was used in this study; Doll[7] and his associates in England and Wales, a rather different method. The latter selected a small random sample of the population and requested each person in the sample to save all the butts he smoked during a specified interval of time. Each of these two methods has certain advantages and certain disadvantages. The advantages of the method used by Doll *et al.* is that it insured a reasonably proportional representation of socio-economic classes, age groups, and occupations. On the other hand, one might raise the question whether a person is likely to smoke in his usual fashion when he is saving his butts for future study. This possible difficulty is avoided by the method we used, but it has the disadvantage that various segments of the population are not proportionately represented. However, we do not believe that this difficulty is of much importance since socio-economic class, sex, and location were taken into consideration.

The average length of butts collected in Canada (27.9 mm.) was just slightly less than the average length of butts collected in the United States (30.9 mm.) On the other hand, the average lengths of butts collected in the Netherlands (20.8 mm.) and in England and Wales (18.7 mm.) were very much less than the average lengths of butts collected in Canada and the United States. It seems most unlikely that such large differences could be accounted for by differences in sampling procedure. The average length of butts collected in Canada varied with socio-economic class, but the average length of even those from the lower class (25.5 mm.) were considerably greater than the average length of those collected in the Netherlands and in England and Wales.

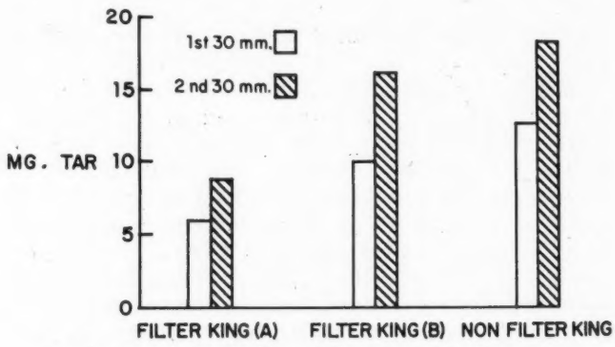

Fig. 3.—Amount of smoke condensate by butt length.

We are not particularly concerned with the reason for the difference between the two North American countries and the two European countries. However, relative to purchasing power, cigarettes are far more expensive in England and Wales than in Canada and the United States, and this may perhaps be the explanation. Whatever the reason, this is one instance in which wastefulness may be more desirable than thrift.

The apparent importance of the butt length of a cigarette in the development of cancer of the lung is at least in part a result of the fact that the latter part of a cigarette contains a greater amount of tar than the first part. In a recent report, Wynder[18] presented some data that showed that there is about 50% more total smoke condensate in the second 30 mm. of a cigarette than in the first 30 mm. (see Fig. 3, which also shows the marked differences in tar content of three different popular brands of American cigarettes). In addition to the fact that there is more tar in the latter part of a cigarette, there is some evidence that, on a gram-for-gram basis, the amount of higher polycyclics may be greater in the latter part of the cigarette. This is perhaps a result of repyrolysis. Studies by Lindsey indicate more 3:4-benzpyrene in the cigarette smoke condensate obtained from a cigarette smoked down to 15 mm. as compared with one smoked to 35 mm.[19] Thus, from the point of view of total tar content, as well as from that of higher polycyclics, the smoke of the latter part of a cigarette is probably more carcinogenic than that of the first part.

Biological studies comparing smoke condensates from cigarettes smoked half way down with condensates from cigarettes smoked much farther down suggested that, on a gram-for-gram basis,

the latter was somewhat more carcinogenic. However, these studies were not in themselves conclusive.[20] Such biological studies are not likely to reveal relatively small differences that could be determined by chemical studies. This holds true particularly for this experiment because the cigarette smoke condensate from the second half was mixed with that of the first. It is clear, however, in view of studies of the dose-response relationship with cigarette smoke condensate, that if the lower tar yield of the first part of the cigarette had been considered, the biological activity of the cigarette smoked to the half-way mark would have been significantly less than that smoked to a shorter length.

For the various reasons listed in this discussion, butt lengths should be considered when estimates are made of the exposure of various population groups to cigarette smoke. It may be that the high lung cancer death rate in England and Wales as compared with the United States and Canada is due in part to differences in the average consumed length of cigarettes in these countries. Likewise, differences in the average consumed length of cigarettes may partly account for socio-economic differences in lung cancer death rates.

SUMMARY

A total of 6428 discarded cigarette butts was collected and measured in Montreal, Toronto, Vancouver, and Hamilton. They were classified by type and length of cigarette, location, socio-economic class, and sex of the smoker.

The mean length of all the butts was 27.9 mm. This is slightly less than the reported mean length of cigarette butts collected in the United States (30.9 mm.) but much greater than the mean length of cigarette butts collected in England and Wales (18.7 mm.), and in the Netherlands (20.8 mm.).

The mean length of the cigarette butts was greater for those collected from the upper socio-economic classes, intermediate for those collected from the middle classes, and least for those collected from the lower classes. Of butts collected from the upper classes, 59.4% had filter-tips; of those collected from the middle classes 61.3% had filter-tips; and of those collected from the lower classes 44.4% had filter-tips.

The mean length of butts discarded by women did not differ significantly from the mean length of those discarded by men. There was also little difference between men and women in respect to the percentage of filter-tip cigarettes smoked. In general the butts from filtered cigarettes were slightly longer than those from regular cigarettes, although the difference was not statistically significant.

The average amount of tobacco consumed per cigarette appears to be roughly proportional to the original length of the cigarette.

Smoke from the first part of a cigarette contains proportionally less tar than smoke from the latter part of a cigarette. Therefore, dosage of tar increases rapidly with the amount of a cigarette consumed. For this reason, we suggested that average butt lengths be taken into consideration when estimates are made of the average exposure of various population-groups to cigarette smoke. The differences in average butt length may partially account for reported differences in lung cancer death rates in various countries and various socio-economic classes.

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RESULTS OF INTERMITTENT STREPTOMYCIN THERAPY IN PULMONARY TUBERCULOSIS

The dosage of streptomycin when used intermittently (two or three injections per week) in combination with daily isoniazid or PAS is generally inadequate and invites therapeutic failure, resulting in the excretion of organisms resistant to one or more of the principal antimicrobial agents. Saliba *et al.* (*Dis. Chest*, 36: 49, 1959) call attention to the conclusions of papers that have been published to confirm the earlier findings of the British Medical Research Council: that intermittent streptomycin with daily isoniazid or PAS is not the treatment of choice in tuberculosis. One hundred and eight consecutive admissions to the National Jewish Hospital since 1956 are reviewed, whose sputum was initially positive for typical *Mycobacterium tuberculosis*, and whose previous antimicrobial therapy had included intermittent streptomycin (1 g. two or three times per week). Positive cultures on admission were found in 79%, and all but five were excreting high proportions of tubercle bacilli resistant to streptomycin and/or isoniazid. In 21% the treatment had been apparently successful and the sputum tests were consistently negative for tubercle bacilli.

The authors conclude that intermittent streptomycin should not be used in moderately advanced or far advanced tuberculosis. If it is desirable to avoid daily injections in patients with minimal disease, one should use daily isoniazid with PAS, since this combination has been proved more effective than intermittent streptomycin with isoniazid or PAS. One should not be lulled into believing that high-dosage isoniazid might permit the use of intermittent streptomycin; such a combination has equal numbers of treatment failures.

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MASS PRODUCTION IN MEDICINE

From time to time, medical philosophers warn us about the tendency towards the introduction of the assembly-line into the practice of medicine. Not only do some of them complain that in countries with a widespread social security system, assembly-line medicine is the order of the day, but they see even in the so-called "free enterprise" countries a trend towards mass production. It should be added that those who discuss this topic are almost universally against it. Although they tolerate without a murmur and indeed almost without noticing it the fact that many aspects of their lives have become depersonalized, they are not prepared to tolerate this in the relationship between the doctor and the patient.

Our Dutch contemporary *Medisch Contact* has recently studied in a leading article the question whether in fact medicine is becoming assembly-line work. They agree that this is a problem and they think that the causes which had led to this phenomenon are complex and multiple. Some of these causes will be obvious to anyone. It is clear for example that medicine can do very much more for a patient than it could a few decades ago; doing things for people takes time, and it may be that complicated technical procedures are now occupying the time previously devoted to the conversation between doctor and patients which many consider the real essence of therapy.

Furthermore, the public is more enlightened; the public knows about advances in medicine, knows that many conditions previously neglected can now be dealt with, and comes to the physician expecting help for things it previously would not have bothered about. Another factor is the increasing average age of the population in the highly developed countries which has increased the load of medical care, since older persons tend to require more care than younger ones. A further factor is the ease of general communication. In the old days when getting the doctor meant an uncomfortable ride or a walk over a considerable distance, only serious illnesses tended to obtain attention. Now that the telephone and other modern means of communication are available, trivialities also come into the physician's purview.

A factor which some persons would put at the top of the list is the fact that it is now easier to pay the doctor; in many instances the development of health insurance and other social security measures has meant that persons whose pride or fear of debt restrained them from seeking medical aid are now doing so.

Lastly, there is the question whether, in this modern world, members of the community are under greater stress than they were in years gone by, and whether these stresses and strains of their lives cause them to seek advice from the physician. This is a debatable point, and there are not wanting voices which proclaim that we are under no greater stress than some of our forefathers were, but that the nature of the stress has changed. It must not be forgotten too that the doctor for many decades has been regarded not only as a medical consultant, but as a source of wise advice on a great variety of life's problems. It may be that the calls upon him have diminished in recent years with the growth of other social agencies to help mankind over the various hurdles of life.

Analysis of the factors tending to mass produce medical care takes no account of course of the fact that a great volume of sickness has actually disappeared in a country like ours, and that the doctor has now much time at his disposal which he formerly required to deal, for example, with the great mass of infectious disease.

Persons who complain about mass production in medicine seem to forget that this is a generalized phenomenon in modern life. Many personal services have now become impersonal services. The impersonal chain store has taken over the place of the personal attention given by the local grocer, butcher and baker. The impersonal laundry has taken the place of the legendary Irish washerwoman; and the TV dinner and the tin, of her equally legendary colleague, the Irish cook. The pharmacist no longer compounds an elegant blunderbuss prescription, personally delivered to the local dignitary's house; a few pills counted out across the counter have replaced this service, and Molière's apothecary no longer rushes into the bedroom with a large enema syringe.

Yes, indeed many personal services have gone, apparently forever, and only a few romantic souls miss them. But it is well to remember that the relationship between patient and doctor remains unchanged, and that you don't have to be very romantic to prefer a humane and sympathetic figure with time for listening to your complaints to a slick, highly efficient technical robot surrounded by gadgets and labour-saving devices but a poor supply of the milk of human kindness. As long as we bear this in mind, and watch for signs that we are turning into assembly-line workers, we shall not go far wrong.

Editorial Comments

AN ORAL DIURETIC WITH PROLONGED ACTION

A new diuretic agent, Hygroton or 1-oxo-3-(3′-sulfamyl-4′-chlorphenyl)-3-hydroxy-isoindoline, synthesized by Geigy Ltd., Basle, Switzerland, and two others of related chemical structure are the subject of three papers, two of which deal with the pharmacological effects and the third with the clinical experience. Stenger, Wirz and Pulver, of the Geigy laboratories, report on the chemistry of these agents and compare them with the older diuretics of this group such as acetazolamide and chlorothiazide.[1] Although Hygroton inhibits carbonic anhydrase, this activity is only one-eleventh that of acetazolamide and does not appear to have any relationship to its diuretic action. In dogs, oral or intravenous administration of this drug produced pronounced and prolonged effects on excretion of water and sodium. This action of Hygroton is not influenced by experimentally produced acidosis or alkalosis and can still be observed 13 hours after administration. In dogs, its toxicity was extremely low, the average lethal dose being 5 g./kilogram. Rats receiving extremely high doses showed no signs of toxicity over a period of four weeks. Its site of diuretic action is believed to be in the tubules, and the action is presumed to be due to inhibition of sodium reabsorption.

In a second paper by the same authors the fate of Hygroton in the body is described.[2] Although practically completely absorbed after oral administration, the drug's absorption was slow owing to its low solubility. Markedly high and prolonged concentrations of the drug were present in the kidneys, while in other organs the concentration did not persist to such an extent. None of the drug was found in fatty tissue or in organs rich in lipids. In the dog, 90% of the intravenously administered drug was excreted unchanged in the urine within 24 hours. The authors describe a spectrophotometric method for the assay of this drug in the blood, urine and tissues.

The final paper by Veyrat, Arnold and Duckert of Geneva describes experiences with Hygroton in five normal persons and in some 100 patients with œdema or ascites.[3] In the normal subject a single dose of 25 milligrams increased sodium excretion by 140%, as compared to other days. Excretion of chloride is approximately equal to that of sodium whereas potassium secretion is minimal. Alkalinization of the urine due to inhibition of carbonic anhydrase is very slight. Its main characteristic is the prolonged action which can still be noticed in healthy subjects after 24 hours. In the patient with œdema, its effect is marked for at least 24 hours, sometimes for over a day after that. In doses from 100 to 600 mg. it has been found very effective as a diuretic, and is considered by these authors to be superior to all the other oral diuretics hitherto employed. Its action on chronic glaucoma is similar to that of acetazolamide but, because of its only slight alkalinizing action, it does not favour the development of renal lithiasis. It is well tolerated and the only undesirable side effect observed by these authors was a loss of potassium and transitory hypokalæmia in patients predisposed to developing this condition.

It is suggested that œdema which is easily mobilized be treated with a single dose of 100 mg. and, in cases where sodium excretion is low and the weight remains unchanged in spite of a low-sodium diet, a single dose of 200 mg. be given. This is repeated after the effect of the dose has worn off, and usually two doses a week suffice. If the first dose fails to produce any effect, a doubling of the dose may be tried. In case of failure, further increase of the drug is useless. Hypokalæmia is easily overcome by administration of potassium as citrate or fruit juices in 40 mEq. doses daily or every second day. This is particularly important in cirrhotics and in cardiac patients with arrhythmias sensitive to digitalis.

One might wonder whether the prolonged action of this obviously very efficacious diuretic is truly advantageous. In many patients with œdema, prolongation of diuresis throughout the night interferes with sleep and is not altogether desirable. Furthermore, daily administration of a tablet is more likely to be complied with regularly by most patients than administration at longer intervals. On the other hand, the single dose, which has the efficiency of a mercurial diuretic without its undesirable features, cannot fail to be welcomed. Well-regulated cardiac patients with œdema might adjust the frequency of medication themselves, according to their gain in weight after a basal dry weight has been established according to the principles of Gold in treatment with mercurial diuretics. In any case, the addition of a new and effective diuretic is worth while. As is the case with other pharmacological agents, this new drug will no doubt prove effective in certain cases and not in others.

W. GROBIN

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AN ASSOCIATION OF LIBERAL PROFESSIONS

Our colleagues of the Swiss Medical Association have recently had a good idea, which will be watched with interest. It occurred to them that many of the problems in this day and age confronting the medical profession might well be affecting the other so-called "liberal professions", so they organized an informal working group to discuss mutual problems. The working group consisted of representatives of the following associations: the Swiss Federation of Lawyers, the Swiss Society of Pharmacy, the Swiss Society of Engineers and Architects, the Swiss Society of Veterinarians, the Swiss Society of Dentistry and the Swiss Medical Association. A preliminary exchange of views was followed by a number of further meetings at which it was agreed that the working group should not be representative of all the walks of life requiring a university training, but simply of those professions which might be expected to have something in common as regards their work and their interests.

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The first step was to exchange information. Members of one profession are notoriously ignorant of the activities of others. For instance, as the veterinarians pointed out, they themselves were not—as many persons imagined—simply doctors to sick animals but rather economists with a knowledge of medicine. In a recent issue of the Swiss medical bulletin (*Schweizerische Arztezeitung*, 40: 491, 1959) the various professional associations outline the present situation of their profession in Switzerland and the problems with which they are confronted. Various common grounds for discussion become apparent after reading these short accounts. Thus for example the lawyer is as much bound to professional secrecy as the doctor, and he is answerable not only to the state but very much more to his professional organization for his conduct. Hence, there must be common ground for discussion of ethical problems. Several of the organizations stress the belief that in the modern world the work of the professional man tends to be undervalued by the community. They also say that as a result of this and of associated economic penalties, recruitment for their profession is not in a satisfactory state. Problems of recruitment might therefore be jointly discussed.

The engineers and architects note that their association has now reached the stage where not only the qualifications of prospective members are looked at but also their standards of behaviour. Some professions feel that there is a need to add to their already rather long curriculum, but do not see how to do this. Others remark that certain areas of their work are being encroached upon by other less qualified persons.

All in all, it would seem that something of value may emerge from these meetings, particularly in view of the fact that the federal government in Switzerland has already acknowledged the existence of this new group, which in time may exert national influence.

THE EPIDEMIOLOGY OF SMOKING

Like the literature on alcohol consumption, the literature on tobacco smoking has increased greatly in volume of recent years, mainly because of the weight of evidence that cigarette smoking in particular is related in some way to the development of lung cancer. Nevertheless, it seems that in spite of the mighty blast that James I of England loosed against tobacco well over 300 years ago, and the recent pronouncements of scientists, a high proportion of Britons and North Americans still patriotically assist their governments to balance their budgets by the use of this homely drug.

Two recent surveys of the distribution and development of smoking habits concern populations in the United States and in Scotland respectively. The U.S. survey[1] is concerned entirely with cigarette smoking among high-school students. It includes some baffling statistics and indicates the complexity of the situation. It was comparatively easy to show that, as might have been expected, children from homes where the parents smoked were more liable to smoke themselves. It would seem that, even in this degenerate age, parental example is still of some educational value. The survey suggested also that students who participated only a little or not at all in extracurricular activities tended to smoke more than those who were involved in athletics or other social diversions. Furthermore, there seemed to be a correlation between cigarette smoking and scholastic achievement; the less successful student with lower academic goals tended to smoke more than his more talented and ambitious brother. One puzzling finding was that a much higher proportion of students from Roman Catholic schools smoked than did their Protestant confreres.

The British survey[2] is concerned on the other hand with adults over 21 years of age. Of these, it seems that no less than 74% of men were currently smoking as against 37% of women. As in the American survey, there was a very definite correlation with intellectual attainment. The highest proportion of smokers was among the unskilled and semiskilled manual workers, while the least was among professional and office workers. Moreover, the less successful persons in society tended to smoke more heavily, while they also tended to start younger. As in some United States studies, the authors note an association between non-smoking and such characteristics as industriousness, ambition, asceticism and religious observance. Moreover, there was a close correlation between the use of alcohol and of tobacco. It would seem that Bernard Shaw's "middle-class morality" is still a prominent factor in the mores of Scotland.

Statistics on the giving-up of smoking confirmed what all smokers know, namely, that many smokers give up the habit at frequent intervals. It would be nice to think that the comparatively low incidence of smoking in middle-aged professional men in the Scottish survey was due to fear of lung cancer, but it seems that this is not the case. The commonest reason given for ceasing to smoke was financial, and of those who gave health as the reason, few were at all concerned about the possibility of contracting a lung cancer. It should be added, however, that nearly one-half of all smokers maintained that they would like to give up smoking if they could do so easily. Perhaps the Departments of Inland Revenue and Health Education can between them devise a means for helping these unfortunates to attain their wish.

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TIME AND THE NERVOUS SYSTEM

"It is possible that a comprehensive description of disorders of the time sense will contribute towards the solution of certain difficult problems, such as 'consciousness', 'memory', 'localization of function'. Work in progress appears to be directly connected with the technology of high-speed flying and four-dimensional geometry. Aeronautical scientists already appreciate the need to understand principles of nervous activity and function.

"The subject of the personal time sense has become the concern of several branches of science. In neurology we have passed that moment of government time [clock-on-the-wall time] when a static three-dimensional concept of nervous function can satisfy the needs of scientific advance."—W. Gooddy: *Lancet*, 2: 1156, 1959.

Medical News in brief

BLOOD PRESSURE LOWERING EFFECT OF PYRROLIDINOMETHYL TETRACYCLINE IN PYELONEPHRITIS

Intravenous treatment of pyelonephritis with pyrrolidinomethyl tetracycline (Reverin) lowered a high blood pressure to normal or near normal values in 29 out of 71 selected cases. Bohn and Koch (*Deutsche med. Wchnschr.*, 84: 1724, 1959) who report these results state that the lowering effect was maintained as long as treatment was continued but persisted in seven patients for some time afterwards. In three patients the blood pressure remained at its normal level over a two-year period of observation. In two patients, retinopathy and in one even microaneurysms of the eye grounds disappeared as a result of treatment.

Whilst this beneficial effect was achieved in two-thirds of all male patients, it was obtained in only one-third of all female patients. This may have been related to the fact that in this series diabetes was present three times as frequently among females as among males. In general, pyelonephritic hypertension of diabetics is far less amenable to treatment. Pyelonephritis with hypertension of long duration is obviously far more resistant to treatment than a similar condition of very recent onset, in which elimination of bacterial foci may lead to complete cure or to marked improvement. It is of interest that in some of these patients oral administration of tetracycline was without effect whereas intravenous injection of Reverin led to normalization of the blood pressure.

SURGICAL TREATMENT OF HYPERKINETIC DISORDERS

Parkinsonian tremor and rigidity can be altered, diminished or abolished by surgery of the basal ganglia. However, many characteristics of the Parkinson syndrome are unaffected by surgical efforts. Although these operations have been accomplished in most cases without difficulty, they may be hazardous because of danger to life and to motor function; if performed on the dominant side, they may markedly affect personality, mentality and speech function. Mayo Clinic authors (*Proc. Staff Meet. Mayo Clin.*, 34: 343, 1959) therefore recommend this type of surgical treatment cautiously. They feel that patients who are mentally or physically deteriorated cannot be benefited appreciably by surgical means and therefore prefer to select candidates for surgical treatment who are not completely disabled, with one side less affected than the other, and with tremor and rigidity as dominant factors. They favour operating on the non-dominant hemisphere and not bilaterally. Most patients who underwent such surgical treatment had Parkinson's syndrome, though the authors have operated on patients with other disorders of movement, but without sufficient numbers to comment on their experience. They have also had no clinical experience in using ultrasonic energy or radioactive material to produce these lesions, and consider such efforts to be still in the investigative stage.

INTRAPERITONEAL INJECTION OF BLOOD

Although it is often assumed that signs and symptoms of a ruptured ectopic pregnancy are produced entirely by intraperitoneal bleeding, such factors as distension and rupture of the fallopian tube, and adhesion of omentum or loops of bowel, cannot be ruled out as contributing factors. Keettel of Iowa City (*Am. J. Obst. & Gynec.*, 78: 1324, 1959) studied the effects of injection of blood and electrolyte solutions into the peritoneal cavity in women through a needle inserted into the posterior cul-de-sac. Amounts of blood up to 650 ml. and of saline up to 1800 ml. were injected over periods of four to 24 minutes.

It was found that citrated blood injected into the peritoneal cavity through such a puncture produced transient lower and upper abdominal cramps, often accompanied by shortness of breath, belching and rectal pain. When the abdomen was opened one to eight days later for another purpose, most of the blood was found to be absorbed but the bowel and omentum were coated with a thin film. Biopsy of the pelvic peritoneum showed chronic inflammation.

When saline solution was injected by the same route, few if any symptoms were encountered and there were no physical changes. When unmodified blood was injected, symptoms and results of examination were minimal and persisted for only a few minutes. At operation later, there was no coating of viscera and only slight tissue reaction. General changes were also found to accompany injections; these included a transient leukocytosis and rise in erythrocyte sedimentation rates.

The authors note that blood injected into the peritoneal cavity in large amounts undergoes concentration; some intact cells gain access to the peripheral circulation but there is marked hæmolysis and absorption of free hæmoglobin. This route is not recommended for transfusions.

STERCORACEOUS ULCERS OF THE COLON

Dried or impacted fæcal contents may, through pressure, cause ulceration of the mucosa of the colon and rectum, and the term stercoraceous ulcer has been applied to these lesions, which may progress to perforation of the intestinal wall. In an autopsy study of these lesions, Grinvalsky and Bowerman of Chicago (*J. A. M. A.*, 171: 1941, 1959) point out that this subject has been very little discussed in the literature. They found that in 175 unselected autopsy examinations, there were 10 cases of stercoraceous ulcer. In four cases this led to perforation, secondary peritonitis and death. In six cases constipation had been recorded, and in two diarrhœa with bright red blood flow from the rectum. In eight of the 10 patients the ulcers were limited to the rectosigmoid area and in three patients there was only one ulcer. They ranged in size from 2.5 to 10.7 cm. in diameter.

It appears that stercoraceous ulceration does not commonly occur in the presence of normal bowel function, but is particularly liable to be found in elderly or bedridden patients with constipation and malnutrition.

(Continued on advertising page 43)

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NEW DRUGS

This listing of new products is based on information received from Dean F. N. Hughes, Faculty of Pharmacy, University of Toronto, and the *Canadian Pharmaceutical Journal*, to whom we owe thanks.

MISCELLANEOUS

TIGAN 'Roche' (Ro/2-9578—antiemetic)

Description.—Contains as active substance 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride; available for oral, parenteral and rectal administration.

A specific antiemetic; blocks the emetic mechanism without causing sedation, tranquillization, hypotension or other undesirable secondary effects.

Indications.—Prevention and treatment of nausea and vomiting. Useful in relieving nausea and vomiting due to pregnancy, infections, toxicoses, underlying disease processes, drug administration, radiation therapy and travel sickness. May also be of value in nausea and vomiting during the postoperative stage, in labyrinthitis, Ménière's syndrome or psychic disturbances.

Administration.—Four times daily, or as directed.

	Capsules	*Suppositories*	*Ampoules (intramuscularly)*
Adults and children over 90 lb.	1 or 2	1	2 c.c. (200 mg.)
Children, under 30 lb.	—	½	0.5 c.c. (50 mg.)
30 - 60 lb.	1	½	1 c.c. (100 mg.)
60 - 90 lb.	1	½ - 1	1.5 c.c. (150 mg.)

How supplied.—Capsules, 100 mg. (blue and white), bottles of 100 and 500.

Ampoules, 2 c.c. 200 mg., boxes of 6 and 25.

Suppositories, 200 mg., boxes of 6.

PROFENIL, Gravet

Description.—Bis-gamma-phenylpropylethylamine.

Indications.—As an antispasmodic.

How supplied.—Boxes of 6 and 50 ampoules, 1 c.c. Boxes of 12 suppositories, for adults or children. Bottles of 100 suppositories, for adults or children.

Also available in Forte form.

How supplied.—Bottles of 20, 100, 500 and 1000 tablets; boxes of 6 and 50 ampoules, 2 c.c.

Pentaerythritol tetranitrate: P-T 10, Dymond

Description.—Tablets of 10 mg.

Indications.—Of use in the management of angina pectoris. Effective in reducing the frequency of attacks and the nitroglycerin requirements.

Administration.—Usual dosage—3 to 4 tablets daily before meals.

How supplied.—Bottles of 100, 500 and 1000.

Rauwolfia and nitrate: P-T RAUWOLFIA (Pr), Dymond

Description.—Each tablet contains: pentaerythritol tetranitrate 5 mg., rauwolfia extract (alkaloids 0.4 mg.) 10 mg.

Indications.—Angina pectoris and hypertension.

How supplied.—100, 500 and 1000.

Silicone barrier cream: PROTECTO-DERM, I. & B.

Description.—Polymerized dimethyl polysiloxane in vanishing-cream base.

Indications.—A silicone "barrier" cream which forms an invisible, greaseless, non-sticky, water-repellent film. Preventive therapy for occupational dermatoses, inflammation caused by body fluids, chafing, chapping, fissures, etc.

Use.—Apply to the dry area to be protected and rub well into the skin. May be applied as often as necessary without removing previous applications. Because of its occlusive nature, it should not be used when skin is acutely inflamed or infected.

D-Calcium pantothenate: PANTHOJECT, U.S. Vitamin

Description.—Injectable solution of d-calcium pantothenate, 250 mg. per c.c., for intramuscular use.

Indications.—In prophylaxis and treatment of postoperative abdominal distension, intestinal atony and paralytic ileus.

Administration.—Intramuscular injection of 1 c.c. (250 mg.) preoperatively and/or immediately following intra-abdominal surgery. Repeat every six hours until normal intestinal motility is restored.

How supplied.—10 c.c. multiple dose vials, boxes of 6.

ANALGESICS

Carisoprodol: SOMA, Wallace Labs.; RELA, Schering

Description.—N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate, possessing an unusual analgesic and muscle relaxant action. Said to modify central perception of pain without abolishing peripheral pain reflexes; it also has a mild antipyretic action.

Indications.—Pain, spasm and stiffness in a variety of inflammatory, traumatic and degenerative conditions affecting muscles and joints and including: arthritis, osteoarthritis, rheumatoid arthritis, periarthritis, spondylitis, lumbosacral and sacroiliac strain, sprains, whiplash injuries, intervertebral disc syndrome, bursitis, torticollis, fibrositis, fibromyositis and tenosynovitis. Also for relief of postoperative myalgia. To normalize motor activity in neurological disturbances such as cerebral palsy and other dyskinesias characterized by abnormal reflex activity, increased muscle tone, involuntary movements and incoordination.

Administration.—Usual adult dose one 350 mg. tablet three times a day and at bedtime; usual dose for children, 5 years or over, one 250 mg. capsule two or three times a day.

Side effects.—Said to be of low toxicity. The only common side effect is sleepiness with higher than recommended doses.

Meprobamate-benactyzine: DEPROL, Wallace Labs.

Description.—A combination of meprobamate with benactyzine, i.e. of a central nervous system relaxant with an anticholinergic. Each tablet contains 400 mg. meprobamate and 1 mg. benactyzine.

Indications.—All forms of depression, both acute and chronic: endogenous depressions and less severe depressions associated with anxiety states.

Administration.—One tablet four times a day, increasing if necessary to three tablets four times a day with later gradual reduction to maintenance levels.

Side effects.—May produce drowsiness in some patients; allergic skin reactions have been observed, occasionally accompanied by fever, nonthrombocytopenic purpura, angioneurotic œdema, hypotension and bronchial spasm. Careful supervision advised, especially for patients with a known propensity for taking excessive quantities of drugs.

Phenylbutazone: STERAZOLIDIN, Geigy

Description.—A combination consisting of Butazolidin (phenylbutazone) 50 mg., prednisone 1.25 mg., aluminum hydroxide 100 mg., magnesium trisilicate 150 mg. and homatropine methylbromide 1.25 mg.

Indications.—Arthritis and allied disorders.

Administrations.—Dosage should be individualized. In acute therapy dosage should not exceed 12 capsules on the first day and 6 to 8 capsules on succeeding days. In chronic therapy dosage should not exceed 6 capsules a day and must be tapered off gradually to establish the minimum maintenance level.

Contraindications.—The same as for steroid or phenylbutazone therapy alone. Should be used with great care in the elderly and preferably avoided altogether in the frankly senile patients.

How supplied.—In bottles of 30 and 100.

MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films. The films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 1762 Carling Ave., Ottawa 3, Ontario. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

MISCELLANEOUS

Motile Spermatozoa as an Index of Fertility in Man—1948; Silent; B & W; 11 minutes.

Produced by Edmond J. Farris, Wistar Institute of Anatomy and Biology.

Description.—A research-record-instructional film, defining an index of fertility in the male, based upon the number of moving sperms in an ejaculate.

Appraisal (1949).—This film is the "clinical" follow-up to a film on sperm counting by the same author (a technique for counting motile spermatozoa). It is a clear presentation, enhanced by some beautiful phase-microscopy sequences. Recommended for medical audiences such as specialists in the subject matter, general practitioners and medical students in the clinical years. Suitable for pre-clinical students and interested scientific audiences. Inappropriate for most other groups.

Availability.—National Medical and Biological Film Library ($1.50). For purchase apply to Dr. Edmond J. Farris, Wistar Institute of Anatomy and Biology, Woodland Avenue & 36th Street, Philadelphia 4, Pa.

Oxyuriasis—195-; Silent; B & W; 20 minutes.

Produced by the Institute of Hygiene, Faculty of Medicine, Montevideo, Uruguay, South America.

Description.—This silent film, with subtitles in Spanish, deals with the pinworm and relies mainly on animated models and diagrams to demonstrate the anatomy and embryological development of the parasite (*Enterobius vermicularis*) and the epidemiology and symptomatology of the condition. The film also shows the diagnostic technique and mentions prophylaxis.

Appraisal (1957).—Although the film is silent, with subtitles in Spanish, the techniques of presentation are sufficiently effective to make it understandable by viewers with no knowledge of the language. The parasite considered is extremely common in children in Canada, as elsewhere. The film, though rather ragged cinematically, is in the opinion of the appraisal panel the best account of the parasite yet seen. The prophylactic and therapeutic measures shown are rather weak, but it remains a good teaching film for medical students in the preclinical and clinical years and for nurses. Also suitable for technicians and medical auxiliaries and general scientific audiences.

Availability.—National Medical and Biological Film Library ($2.00). For purchase apply to the producers.

Cardiac Arrest—1957; Sound; Colour; 17 minutes.

Produced by Verity Films (Oswald Silbeck, M.A.) for Imperial Chemical Industries Limited. Technical Advisers: John Beard, M.D., F.F.A., The Post-Graduate Medical School of London.

Description.—This instructional-training film sets forth a technique for dealing with cardiac arrest by opening the chest wall and massage. Causes of cardiac arrest are discussed and massage is shown on a model of the heart. A sudden, naturally occurring arrest is shown in an elderly person and the circumstances under which cardiac massage would result in a successful outcome are discussed. The various steps of the technique are outlined in detail, in the case of a young subject going into arrest after induction of anæsthesia. Emphasis is put on speedy institution of a predetermined sequence of actions designed to produce a circulation within three minutes. The anæsthetist is seen performing the thoracotomy and instituting massage until surgical assistance arrives. The place of drugs is discussed. A heart in fibrillation is seen and restoration of a normal rhythm observed.

Appraisal (1958).—The film is a well-produced and logically developed presentation of the current thinking on both the causes for and treatment of cardiac arrest. Recommended for general practitioners doing surgery, for medical students in the clinical years, for nurses and for anæsthetists. It might have been mentioned that it is advisable to have the operating surgeon in the immediate vicinity when anæsthesia is induced.

Unsuitable for non-medical audiences.

Availability.—National Medical and Biological Film Library ($3.00). For purchase apply to Publicity Department, Imperial Chemical (Pharmaceuticals) Limited, Fulshaw Hall, Wilmslow, Cheshire, England.

Childbirth Without Fear—1953; Sound; Colour; 20 minutes.

Produced in South Africa for Dr. Grantly Dick Read.

Description.—Filmed entirely in South Africa where he first observed the ease with which native women gave birth without the use of painkillers, Dr. Grantly Dick Read tells of three cases he has chosen. All three have, of course, prepared themselves for natural childbirth under his direction. In two of the cases the mother had previously experienced difficulty in childbirth, one of the two having undergone Cæsarean section.

This film, restricted for use to medical personnel and to special groups only (mothers desiring natural childbirth), is an excellent presentation of "natural childbirth". A good presentation of delivery for prepared women, this is a film for the medical profession—for those who know Dr. Read's teachings, and for medical students in the clinical year and for nurses. May be shown also by obstetricians practising natural childbirth to patients who desire it and who a doctor feels may benefit by it.

Availability.—National Medical and Biological Film Library ($2.00). Purchase (in Canada) from J. Arthur Rank Distributors (Canada) Limited, 277 Victoria Street, Toronto, Ontario.

Direct Artificial Respiration—1959; 16 mm., Sound; Colour; 25 minutes.

Prepared by A. B. Dobkin, M.D., and M. H. Brook, M.D., Saskatoon, Sask. Produced in Saskatoon by the University of Saskatchewan College of Medicine.

Description.—This teaching film shows the comparative effectiveness of the various methods of artificial respiration with a curarized apnœic subject. Techniques of direct artificial respiration are demonstrated in common situations such as drowning, traffic and industrial accidents, and electric shock. A practical method of training and instructing a group in the various techniques of direct artificial respiration is shown, using a manikin and other training aids.

Availability.—Pyramid Film Producers Ltd., Saskatoon, Sask.

Film for Mental Hospital Patients.

A film designed for viewing by mental hospital patients during rehabilitation was selected as a United States entry in the Venice Film Festival, held July 2-12, 1959. "A New Chapter", conceived and sponsored by Smith Kline & French of Montreal and Philadelphia, presents the story of one man's experiences in readjusting to community life after release from a mental institution. It was one of 20 "non-Hollywood-type" films chosen by the Committee on International Non-Theatrical Events (CINE), a voluntary group formed in 1958 for the purpose of co-ordinating U.S. entries in overseas film festivals.

The film is available from: Smith Kline & French International American Corporation, 300 Laurentian Blvd., Montreal 9.

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MEDICAL SOCIETIES

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

As an expression of the growing amount of scientific material available for discussion in Canada, the Twenty-Ninth Annual Meeting of The Royal College of Physicians and Surgeons of Canada occupied for the first time three days instead of the traditional two. It took place in the Queen Elizabeth Hotel, Montreal, on Thursday, Friday and Saturday, January 21, 22 and 23, and attracted a record attendance of fellows and guests.

The pattern was somewhat different from that in former years. The first morning was devoted to registration, a series of addresses of welcome by Senator Sarto Fournier, Mayor of Montreal, and the Deans of Medicine of the two Montreal universities, Drs. Wilfrid Bonin and Lloyd G. Stevenson, followed by the annual business meeting in the ballroom of the hotel. The other two mornings consisted mainly in a series of lectures and demonstrations at local hospitals from 9 to 11 a.m., followed respectively by the annual lectures in surgery by Dr. Rocke Robertson on "Venous thrombosis", and medicine by Dr. K. J. R. Wightman in "The rational era of therapeutics". The afternoon sessions were of a more conventional pattern, with sessions in medicine, surgery and obstetrics and gynæcology; the division of medicine held two concurrent sessions on Friday and Saturday, and the division of surgery held sessions on orthopædic and neurological surgery, and thoracic and cardiovascular surgery respectively, on Friday afternoon.

Each evening also contained some activity. The Mayor and City of Montreal gave a reception to the fellows and guests in the Chalet on Mount Royal on Thursday evening, while the Annual Convocation was held on Friday night in the auditorium of the University of Montreal. On Saturday the President's Reception and the Annual Dinner were held in the grand ballroom.

DIVISION OF SURGERY

Thursday Afternoon Session

The Thursday afternoon session of the division of surgery began with a paper on the intraperitoneal and local use of nitrogen mustard at the time of surgery for gastro-intestinal cancer, given by Dr. J. A. McCredie of London, Ontario. He showed that irrigation of the Walker 256 tumour in rats with various chemicals led to 100% of "takes" with saline as against 5% with a 2% solution of Clorpactin and only 3% with nitrogen mustard. In the human series of 26 patients suffering from gastro-intestinal cancer in which nitrogen mustard had been used to irrigate possible sites of cancer cell contamination, and also left in the peritoneal cavity in an attempt to kill any cancer cells lying there, the first thing that had been established was that the treatment was harmless. The technique did not make the operation more laborious, nor was the patient more ill. In the human series there were no deaths and leukopenia was no problem. There was one major wound infection. It remained to be seen whether this procedure, whose safety had been established, would actually prevent recurrences of cancer.

Dr. J. R. F. Mills of Toronto analyzed his series of 22 cases of islet cell tumour of the pancreas, in which the highest age incidence was 20 to 30 years. Central nervous system symptoms were the commonest and included loss of consciousness with or without seizures. Tumours were equally distributed between the head, body and tail of the pancreas and operations performed included one Whipple operation, removals of adenoma and subtotal pancreatectomy. Complications included formation of pseudocysts, recurrence of adenoma and permanent cerebral damage. The diagnosis is essentially that of hyperinsulinism with attacks of insulin shock during fasting or fatigue or emotional stress, relief of attacks with glucose, and blood sugar levels below 50 mg. % during the attacks. It was necessary to be sure that the patient was not giving himself insulin, and also at operation to search for multiple adenomas. Incidentally, the first of these tumours was diagnosed and successfully removed in 1929 in Toronto.

Dr. T. A. Richards of McGill University described studies in hæmorrhagic shock, and demonstrated the beneficial results of over-transfusion at a level of 15 c.c. per kilogram after reinfusion of shed blood, whereas combining hydralazine with overtransfusion showed no appreciable benefits.

Dr. J. A. Palmer of the Toronto General Hospital discussed the treatment of massive prolapse of the rectum on the basis of 53 cases treated at the Toronto General Hospital during the past 20 years. He said that rectal prolapse had been treated since the days of Hippocrates, who advised holding the patient upside down and shaking him. Moschcowitz obliterated almost entirely the rectovesical or rectovaginal pouch with sutures, regarding the prolapse as a sliding hernia involving that pouch. Roscoe Graham opened the peritoneum and appoximated the medical borders of the levatores ani in front of the rectum as well as excising the hernial pouch or sac. The Moschcowitz-Graham operation had been used at the T.G.H. since 1939 with gratifying results. Twenty-three cases treated this way had shown no recurrence, whereas other procedures had a high recurrence rate. Unfortunately, the problem of incontinence was still unsolved. A possible modification of the operation was the suturing of the pubo-rectalis behind the rectum.

Out of a series of 270 patients with carcinoma of the breast in Vancouver, Dr. L. B. Fratkin had performed selective biopsy on 129 and omitted it in the other 149. A triple biopsy was performed with (1) an incision over the lesion, (2) an incision under the midclavicle after changing all drapes, gowns and instruments, (3) a parasternal incision to obtain nodes from the second and third spaces. If the first biopsy is positive, stage 2 is performed, and if the second is positive the procedure stops. In his series, Dr. Fratkin has encountered only three cases of infection and a few cases of delayed healing. The proportion of cases in which an incomplete biopsy was done is diminishing; there were 36 positive biopsies and 80 negatives in the series. The speaker claimed that all clinical stage 2 and stage 1 with upper or lower inner or central lesions or with lesions over 2.5 cm. in diameter should undergo selective biopsy.

There was vigorous discussion of this paper and it was suggested that triple biopsy should not be used to deny the benefits of radical operation to patients just because one or two apical nodes happened to be positive. Dr. R. M. Janes pointed out in particular that we should be careful about abandoning patients, because the deciding factor was the patient's resistance to her disease.

Dr. J. R. McCorriston of Montreal described three cases of aneurysm of the hepatic artery in which surgical treatment had been successful. The aneurysm had been excised completely, and arterial blood supply to the liver preserved, with the addition of spleno-hepatic arterial anastomoses in one case.

Dr. S. A. Piper of the Toronto Western Hospital gave a further report on a total series of 597 examinations of the biliary system with the intravenous contrast medium, Cholografin. His first series of 228 cases had been published in the *Canadian Journal of Surgery* a couple of years ago. Out of his present total of 216 cases in which biliary disease had been demonstrated by this method, there were 10 cases of error of interpretation. Accuracy was now high, provided that the radiologist supervised the examination carefully. In 114 cases where Cholografin gave a positive result, Telepaque examination had failed. In his new procedure, he took a scout film, then P.A. and oblique P.A. films 10 and 30 minutes and one, two and four hours after the injection, and supervised the whole procedure personally. However, this examination would not replace careful clinical examination in suspected biliary disease.

Dr. J. H. Fisher of Victoria Hospital, London, Ontario, reviewed 19 cases of the unusual tumour known as hæmangiopericytoma, a specific vascular neoplasm composed of pericytes, which occurs in both benign and malignant forms. The tumour usually presents as a painless lump in soft tissues and diagnosis is based on its histological character. Almost all these tumours are malignant and in 42% of cases reported metastases develop and kill the patient. Histological appearance is no guide to malignancy. Local excision invariably leads to recurrence, and a tumour in the deep soft tissues of the leg is particularly dangerous. Of the 19 cases reviewed, nine were treated by operation alone, two by cobalt 60 radiation only, and seven by a combination of these. Ten have apparently been cured.

Dr. Walter C. MacKenzie of Edmonton and his colleagues presented a paper on the effect of local gastric hypothermia on the concentration of plasma pepsinogen in the gastric veins of dogs. They produced local gastric hypothermia by means of an intragastric rubber balloon filled with cold water. In all dogs studied, pepsinogen decreased significantly during cooling and returned to normal after local warming.

A series of 31 cases of primary retroperitoneal tumours collected from the records of Westminster and Victoria Hospitals, London, Ontario, was presented by Dr. J. K. Wyatt. Of the 31 cases, 30 were malignant and 87% sarcomas, the commonest being a reticulum cell sarcoma. Early symptoms were usually lacking and common findings were abdominal pain or gastro-intestinal complaints with a palpable abdominal mass. X-ray findings were positive in over half the cases and pyelography was the most useful radiological procedure. Enormous delay in diagnosis was common. Histological diagnosis was established in 24 cases by biopsy but not until post mortem in four cases. Only three of the 31 cases were operable and the operation mortality was 10%. Some form of radiotherapy was commonly used, cobalt 60 beam therapy being most popular. Prognosis was rather dismal, with six survivors and an average survival time of 23 months. The best palliation was with cobalt 60 therapy.

Orthopædic and Neurological Surgery

On Friday afternoon, the session on orthopædic and neurological surgery began with a paper by Dr. W. R. Harris of Toronto on the density of avascular bone. Dr. Harris felt that current interpretations of the nature of increased density of avascular bone were incorrect. He had studied the matter experimentally in rabbits by producing avascular necrosis of the femoral head and comparing radiographic and histological changes. He showed that increased density to x-rays is uniformly the result of appositional new bone formation on the surface of necrotic trabeculæ and that dead bone itself undergoes no appreciable density change to x-ray.

Dr. J. C. Kennedy of the University of Western Ontario made a plea for consideration of the merits of the Gallie ankle fusion, reviewing 50 cases of ankle fusion out of which 20 had been done by the Gallie method with two slot grafts placed across the ankle mortise. Of the cases 29 were due to trauma, nine to polio, four to tuberculosis and five to osteoarthritis. The results of the Gallie fusions were: 17 satisfactory, two indifferent and one failure. The majority of patients walked well, but there was some unexplained pain.

Dr. J. M. McIntyre of the Montreal Children's Hospital discussed problems in club foot surgery, pointing out how important it was to subject this type of surgery to critical evaluation. He dealt with results in 52 patients over a period of 10 years, 18 with unilateral and 17 with bilateral club foot. He divided his cases into cases of resistant club foot, recurrent club foot and neglected club foot. In the first category, the average age at operation was nine years after trial of non-operative treatment. Surgical results were not satisfactory without tendon transfers. Muscle imbalance was an important factor. In the recurrent cases, good results were obtained from heel cord lengthening, capsulotomy and tendon transfer.

The second half of the session was devoted to neurosurgery, beginning with a paper by Dr. T. J. Speakman on operative treatment of spinal cord injury. Based on an evaluation of 10 years of experience in the treatment of acute spinal cord injury at the University of Alberta Hospital, the speaker demonstrated the value, often misunderstood, of early operative decompression of spinal fracture dislocation. He felt that the degree of recovery after surgical procedures was greater than might have been reasonably anticipated in the absence of such therapy.

Dr. C. Bertrand of Notre-Dame Hospital, Montreal, described his precision method for surgical treatment of Parkinson's disease. He reviewed surgery of 150 cases with a mortality or morbidity rate of less than 2%. Improvement of tremor and/or rigidity ranged between 70% and 90%, and the speaker felt that the operation has now reached a stage when it should be used as soon as the symptoms of Parkinson's disease prevent the patient from carrying on his usual activities. Another lecture on technique was given by Dr. W. Feindel of Montreal, who described the use of radioactive isotopes for studying cerebral circulation. He uses multiple radiation counters applied to the head and neck during intravascular injection of radioactive iodinated human serum albumin given to patients being prepared for automatic brain scanning. The method is still crude but brain circulation times obtained are consistent with subsequently discovered lesions.

Lastly, Dr. T. Jory of Victoria Hospital, London, Ontario, reported on the management of 175 cases of spontaneous intracranial hæmorrhage seen between 1952 and 1959. By means of early carotid arteriography the source of bleeding was identified in 75% of patients. Of the series 97 patients bled from an intracranial aneurysm, 18 from an arteriovenous malformation, and four from a tumour. In 43 cases no lesion was demonstrated by angiography. The series was then analyzed by the speaker, who said that of patients with aneurysms treated conservatively 50% survived, whereas of those treated surgically 70% survived.

Thoracic and Cardio-Vascular Surgery

The session on thoracic and cardio-vascular surgery on Friday afternoon began with a discussion by Dr. M. H. W. Friedman, Edmonton, of the clinical use of polyvinyl sponge (Ivalon) in the repair of œsophageal hiatus hernia. Many authors now feel that such herniæ if they are causing symptoms should be repaired surgically, and the use of prosthetic substances has been recommended to close large defects in the diaphragm. The author described the clinical use of a C-shaped patch of Ivalon sponge in transabdominal repair of œsophageal hiatus herniæ in a series of 15 patients treated at the University of Alberta Hospital. A second paper on the surgery of the œsophagus was given by Dr. E. M. Nanson of Saskatoon, who discussed the œsophageal strictures which may develop from reflux œsophagitis secondary to the sliding type of hiatus hernia. He was particularly concerned with a condition in aged persons, of whom he had seen four males and four females in the last few years. The average duration of their symptoms was five years and in all eight cases the initial diagnosis had been of carcinoma. The correct diagnosis was demonstrated in seven cases by dilating the stricture and obtaining biopsy specimens above and below it. Treatment was by dilatation and a medical regimen and results were satisfactory.

Dr. J. A. S. Wilson of the Royal Edward Laurentian Hospital, Montreal, described experience with 524 pulmonary resections in 500 patients with tuberculosis, done between 1950 and 1958. He showed that resection is a safe procedure even in poor-risk patients if carefully managed, and that although postoperative morbidity is high, it is usually not serious. The majority of patients recovered from their disease (92% are living) and returned to full-time work. Only 2% of patients had died of tuberculosis since operation and 3% of patients had had a reactivation of disease.

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A three-year follow-up survey of 160 femoral and aorto-iliac grafting operations performed for obliterative vascular disease at the Toronto General Hospital was described by Dr. J. A. Key. Results apparently indicate that arterial grafting is a worth-while procedure for patients but that the perfect graft, the ideal technique and the best method of preventing early and late failures have yet to be found. In his report he included results of replacement of the aorta in 71 cases of abdominal aneurysm, and he suggested that this was the most satisfying operation yet available in the field of vascular surgery dealing with complications of atherosclerosis.

Another analysis from Toronto was of a series of 60 repairs of ventricular septal defects at the Hospital for Sick Children, Toronto, reported by Dr. G. A. Trusler. The bubble oxygenator was used, and results had become steadily more satisfactory. Complications included cardiac failure, hæmorrhage, complete heart block, and persistence or recurrence of the defects. Dr. W. Cardozo of the University Hospital, Edmonton, had been studying membrane oxygenation with the use of a teflon sheet with pulsatile oxygen flow. Lastly, Dr. R. O. Heimbecker from the Toronto General Hospital described the preoperative assessment and surgical treatment of congenital aortic stenosis. He felt that this condition is best corrected by direct vision repair using a pump oxygenator. Hypothermia is unsatisfactory because it does not give enough time to deal with the commonly associated subaortic lesion. He described the investigation of nine young adults, seven of whom were subjected to repair under direct vision with the use of the pump oxygenator and also discussed the operative technique.

General Surgical Problems

The Saturday afternoon session in surgery was devoted to discussion of general surgical problems. The first paper was given by Dr. R. A. Mustard of Toronto on the surgical treatment of carcinoma of the hypopharynx and cervical œsophagus. It was in fact a review of all the 42 cases of carcinoma involving the upper end of the œsophagus and treated surgically by Dr. Harold Wookey and the author between 1934 and 1959. Operative mortality was 14% and eight patients had already survived over five years. All but one of the group of long survivals were able to swallow without difficulty, four had their larynx spared and retained normal speech, while others had developed remarkably good pharyngeal speech.

The diversion of the stream of urine into an isolated segment of ileum in 35 cases was discussed by Dr. A. D. McKenzie of the University of British Columbia. In this series there was only one operative death, and results suggested that it was a good method even for palliative purposes. The great advantage of the ileal loop was that active peristalsis keeps the segment empty so that it acts as a conduit rather than a reservoir; ascending infection and reabsorption of electrolytes is thus avoided. The chief disadvantage is of course the need to wear a permanent drainage apparatus. It is too early to decide whether this is superior to formation of a rectal bladder but it is the method of choice where the anal sphincter is incompetent.

Dr. J. P. Bourque discussed colo-cystoplasties versus ileo-cystoplasties. He felt that the sigmoid as a substitute for the bladder had the following advantages. It gave a stronger, thicker and better bladder, its contractile power was greater, it could be placed low in the pelvic cavity and thus remain extraperitoneal, it was less likely to cause bowel obstruction, and it was easy to fashion.

For some years in West Germany, the insufflation of oxygen into arteries in the treatment of peripheral vascular insufficiency has been employed. Dr. Gordon A. Clark of the Westminster Hospital, London, Ontario, began treating peripheral vascular lesions of the legs in March 1959 with this method, which consists of injecting oxygen into the femoral artery three times a week in amounts varying from 20 to 80 c.c. depending on the patient's tolerance. Treatment continues for 6 to 12 weeks and results were certainly very promising in the 50 cases of arteriosclerosis, senile and diabetic, thromboangiitis and post-phlebitic syndrome with ulcer.

An ileo-rectal anastomosis was performed in six unselected cases of ulcerative colitis by Dr. R. H. Thorlakson of Winnipeg, and the follow-up of 3½ years suggests that the procedure has been justified.

Dr. D. A. MacKenzie of the University of Western Ontario described studies made during the past four years with continuous wound suction after operation to eliminate collections of serum and blood. Types of operation in which continuous suction could be employed included mastectomy, repair of ventral hernia, excision of pilonidal cyst, excision of rectum, excision of parotid tumour, amputations, bladder resection and radical gland dissections. Catheters with multiple perforations are inserted into the wound space through a stab wound and low pressure suction applied for 4 or 5 days. Healing is better, wound infections are fewer, skin flaps survive better and there is less tendency to œdema.

Lastly, a critical paper was given by Dr. J. C. Callaghan of the University Hospital, Edmonton, on the safety and value of aortography and arteriography. He and his colleagues had analyzed 100 aortographies and peripheral arteriographies carried out at his hospital since 1956. This series included no fatalities or major complications, and even minor complications were minimal and transient.

Annual Award in Surgery

The annual award of a medal in surgery was made to Dr. Robert Bruce Salter of Toronto, who delivered his paper on an experimental investigation of the effects of continuous compression on living articular cartilage, on Saturday afternoon.

Lecture in Surgery

The annual lecture in surgery was given by Dr. H. Rocke Robertson, Professor of Surgery, McGill University, who reviewed in masterly fashion the difficult subject of venous thrombosis. Dr. Robertson touched on some of the mysteries of experimental induction of thrombosis, pointing out that if thrombi were introduced into healthy veins in animals they simply disappeared. Questions still unanswered were—what causes the propagation of a thrombus? What are the factors promoting thrombosis? There was evidence that changes in the speed of blood flow were a factor in thrombosis, but Quick had said that hypercoagulability was rarely a factor in thrombosis. The third factor left was the vein wall, and Dr. Robertson and his colleagues had established a technique for examining the endothelium of veins after stress. The effects were inconclusive, until the workers devised a technique for inflicting a measured injury on the vein by pressure. The vein wall is extraordinarily fragile and the slightest trauma will cause lesions visible on silver staining of the structure. It has been suggested by this work that minor injuries such as are sustained several times a day by most people, could suffice to cause thrombosis. It is of course difficult to study the effects of trauma on a human vein by the same technique, but the speaker did give an instance in which a blood pressure cuff was blown up and left on an arm and the specimen of vein studied soon afterwards at autopsy, whereupon the vein was found to be filled with thrombus.

It was extraordinarily difficult to diagnose thrombosis because the clinical picture varied from a full-blown one down to the case in which the veins might be full of clot and yet cause no symptoms or signs. He had studied a group of 1000 elderly males who had undergone moderately severe operation. In 842 there were no clinical signs of venous thrombosis but 138 developed one or more of the following—tenderness, œdema, dilated superficial veins, or a positive Homans sign. Yet out of the 842 without physical signs five had a pulmonary embolism and two of these died, while out of the 158 with signs there were six instances of embolism and one death. All this means that it is im-

possible to establish the incidence of venous thrombosis in any series and therefore to assess exactly the effects of treatment. There is very little evidence, said the speaker, to back up the claims made for the various treatments assumed to prevent thrombosis. The weakest point in the therapeutic armour was that there appeared to be no means of preventing the occasional unheralded case of massive embolism.

[*A report of the sessions of the Division of Medicine will be published in our issue of February 20.*—ED.]

1959 FELLOWSHIP EXAMINATIONS OF THE ROYAL COLLEGE

The following candidates were successful in the 1959 Fellowship Examinations of the Royal College of Physicians and Surgeons of Canada.

Medicine (38).—Charles Alexander Adsett, Oklahoma City, Okla., U.S.A.; Donald Oliver Anderson, Vancouver; Claude Robert Augustin Brosseau, Quebec, Que.; Joseph-Jean-Roland Charbonneau, Montreal; Rosario Claveau, Chicoutimi, Que.; Louis Jack Cole, Toronto; Albert Reginald Cox, Seattle, Wash., U.S.A.; Joseph Jean Jacques Crépeau, Beauce, Que.; Yves-Marcel Dagenais, Montreal; Claude Grégoire, Quebec, Que.; Stefan Grzybowski, Toronto; William Michael Hallett, Sudbury, Ont.; Clinton Bruce Hatfield, Calgary; John Gustaf Hellstrom, Montreal; Charles Herbert Hollenberg, Brookline, Mass., U.S.A.; Joseph Paul-Emile André Houde, Jonquière, Que.; Alan Gordon Kendall, Montreal; L. Leslie Kovacs, Montreal; Andrew Koval, Leamington, Ont.; Gabriel C. Laurence, Montreal; Maurice Jean LeClair, Montreal; Glen Alan Lillington, Winnipeg; John Alexander Mills, London, England; George Hamilton Morrison, Fort William, Ont.; Jack Sam Olin, Toronto; Wilfred Howard Palmer, Montreal; John Orval Parker, Bergenfield, N.J., U.S.A.; Jean-Marc Pépin, Sherbrooke, Que.; Francis Isidore Rackow, Croydon, Surrey, England; Ingeborg Charlotte Radde, Toronto; Jack Theodore Ratner, Ann Arbor, Mich., U.S.A.; Burke Alfred Richards, Hawkesbury, Ont.; Hiemie Simon Samuels, Montreal; Gerald Ashton Sears, London, Ont.; Sheldon George Sheps, Winnipeg; Douglas Lorne Thomson, Montreal; Percy Gerald Urback, Toronto; George David Leslie Watt, Toronto.

Medicine (Anæsthesia) (3).—John Michael Reid Campbell, Toronto; Thomas Richard Hanley, Toronto; Leonard Cecil Jenkins, Vancouver.

Medicine (Neurology) (2).—David Purser Jones, Vancouver; Joseph-Louis Raymond Robillard, Outremont, Que.

Medicine (Pædiatrics) (5).—Gerald Hall Holman, Saskatoon; Martin Lindzon, Downsview, Ont.; J. H. Victor Marchessault, St-Lambert, Que.; Rodney John Millar, Cleveland, Ohio, U.S.A.; Mervin Silverberg, Newtonville, Mass., U.S.A.

Medicine (Pathology) (5).—Jean-Claude Boivin, Laval-des-Rapides, Que.; Charles Donaldson Chipman, Halifax, N.S.; William Arthur Harland, Town of Mount Royal, Que.; Louis Philippe Le Gresley, Town of Mount Royal, Que.; Alvin Eli Rodin, Edmonton.

Medicine (Physical Medicine and Rehabilitation) (1).—Paul-André Lachance, Quebec, Que.

Medicine (Psychiatry) (2).—Joseph Herbert Pascoe, Edmonton; Robert Pos, Don Mills, Ont.

Medicine (Diagnostic Radiology) (1).— Salomon Leendert Fransman, Kingston, Ont.

Medicine (Therapeutic Radiology) (1).—Maurice Thibault, Quebec, Que.

General Surgery (53).—Morris Asa, Windsor, Ont.; Ronald James Baird, Toronto; William Henry Barnes, Hamilton, Ont.; Edward James Beaton, Barrie, Ont.; Georges Bédard, Hull, Que.; Sarab Singh Bhatia, New York, N.Y., U.S.A.; Donald Kenneth Black, Regina; Claude Brunet, Quebec, Que.; Frederick William Campbell, Jr., Minneapolis, Minn., U.S.A.; William Stephen Cave, Kelowna, B.C.; Ralph Marenus Christensen, Vancouver; Wallace Bakfu Chung, Vancouver; Gerald Coursley, New Westminster, B.C.; Joseph Stephen David, Toronto; Gordon Russell Davies, Saskatoon; Jean-Paul Després, Quebec, Que.; Joseph-Raymond Fernand Desrosiers, Loretteville, Que.; Robert Orme Farley, St. Thomas, Ont.; Gaston Forget, Montreal; Jacques Bertrand Gagnon, Montreal; Carstairs Clouston Gardner, Oshawa, Ont.; Brian Cameron Gay, Ottawa; Robert Kingsley Graham, Manitouwadge, Ont.; George Yoshinori Hiraki, Toronto; John Donald Hough, Victoria, B.C.; Harry Alexander Hyde, Toronto; Neville James Jackson, Saskatoon; John William Kerr, Kingston, Ont.; Ratan Kumar Keswani, Charlottesville, Va., U.S.A.; Claude Lafortune, Joliette, Que.; Richard A. Lambert, Thetford Mines, Que.; Allan Meredith Lansing, Chicago, Ill., U.S.A.; Louis Joseph Laporte, Ville St-Laurent, Que.; Raymond Denis Joseph LaRocque, Windsor, Ont.; Manly Bernard Levin, Winnipeg; James Forest Lind, Rochester, Minn., U.S.A.; Jacques Alfred Loeb, Toronto; John Duncan Claude Macdonald, Brookfield, Wis., U.S.A.; Ian Donald MacLeod, Weyburn, Sask.; John Andrew McCredie, London, Ont.; Norman Woods Mortimer, Toronto; William Lindsay Ogilvy, Montreal; Radha Krishna Padhi, Kingston, Ont.; Arthur Albert Page, Knowlton, Que.; Charles Roy Palmer, Parry Sound, Ont.; Cyrille Jean Joseph Paquette, Montreal; Sabin Plourde, Quebec, Que.; Terence Alvin Richards, Hamilton, Ont.; Walter Rolland, Brantford, Ont.; Irving Bernard Rosen, Toronto; Ernest Bhasker Sundaram, Montreal; Walter Govan Waddell, Toronto; John Kenneth Wyatt, London, Ont.

Surgery (Neurosurgery) (6).—Antonin Frechette, Trois-Rivières, Que.; Rankin Kilgour Hay, Winnipeg; Sonis Napoléon Martinez, Montreal; Kenneth William Ellis Paine, Saskatoon; Ronald Reginald Tasker, Toronto; Gordon Bruce Thompson, Montreal.

Surgery (Obstetrics and Gynæcology) (23).—Kenneth Baker, Edmonton; Cecil Ronald Bradford, Winnipeg; John David Cairns, Toronto; John Alexander Carmichael, Regina; Jacques Corbeil, Verdun, Que.; Bernard Allan Davis, Montreal; Robert Findlay Edington, Cornwall, Ont.; William Gordon Francis, Toronto; William Denis Fraser, Montreal; Ashley Milton Krisman, Vancouver; Jules Eugène Leclerc, Quebec, Que.; Samuel Librach, Toronto; Robert King Miller, Oshawa, Ont.; Ely Ravinsky, Willowdale, Ont.; Martin Lyle Robinson, Toronto; John Walter Fraser

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Scrimgeour, Fort William, Ont.; Narinder Nath Sehgal, Ottawa; Thomas John Sheppard, Peterborough, Ont.; Stuart Donald Sims, Toronto; William Langford Tew, London, Ont.; Charles Peter Vernon, Toronto; James Garnet Courtland White, Brantford, Ont.; William George Whittaker, Peterborough, Ont.

Surgery (Ophthalmology) (1).—Samuel Walter Nevil Gibson, South Burnaby, B.C.

Surgery (Orthopædic Surgery) (12).—Jean-Claude Caron, Paris, France; William Gerard De Haas, Calgary; Fergus Albert Ducharme, Ottawa; John Graham Evans, Toronto; Michael Clement Hall, Toronto; George Davidson Kay, Toronto; Paul Mailhot, Montreal; Kenneth Alan McCluskey, Doncaster, Ont.; Yves Normand, Trois-Rivières, Que.; Bruce Guy Sadler, Sillery, Que.; Albert McMurdo Sinclair, Halifax, N.S.; Alan Murray Wiley, Toronto.

Surgery (Otolaryngology) (1).—George Shimo-Takahara, Montreal.

Surgery (Plastic Surgery) (2).—Pierre Paul Gagnon, Quebec, Que.; Edward Michael Gold, Montreal.

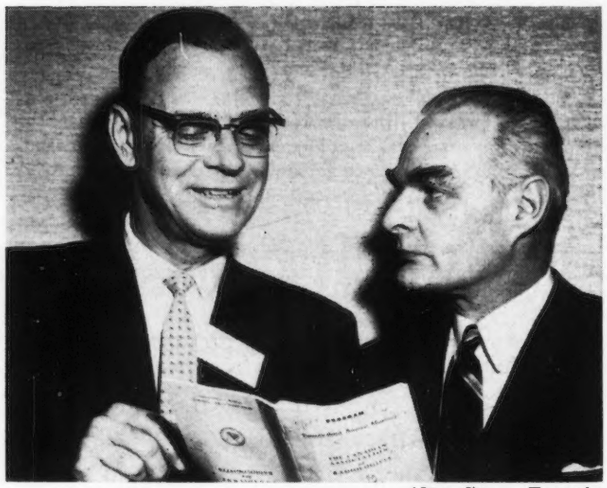
Surgery (Urology) (5).—Neil Calvert Carruthers, Sarnia, Ont.; Gordon Leath Henderson, Windsor, Ont.; Calvin Clarence Krause, Brooklyn, N.Y., U.S.A.; William Hall Lakey, Ann Arbor, Mich., U.S.A.; Laureat J. E. Tremblay, Chicoutimi, Que.

CANADIAN ASSOCIATION OF RADIOLOGISTS

The Canadian Association of Radiologists held their Twenty-third Annual Meeting at the Royal York Hotel, Toronto, on January 24 to 27. The executive of the society had met on Saturday, January 23, and Sunday January 24 was devoted to meetings of council, followed by open house and a buffet supper tendered by Dr. and Mrs. A. McGee. On Monday morning the meeting of council continued, and Monday afternoon was devoted to scientific sessions.

At the Monday afternoon session, Dr. J. S. Dunbar of Montreal described studies which demonstrated that in certain infants with stridor, wheezing and cough, a tracheal narrowing demonstrable on x-ray was largely or entirely due to an infolding of the posterior wall of the trachea during expiration and early inspiration. Dr. N. H. Aldridge of Sarnia discussed the significance of œsophago-gastric invagination, 45 cases of which he had noted in a series of 1400 upper gastro-intestinal series. Drs. B. J. Shapiro and A. A. Track of Toronto described three cases of pneumatosis cystoides intestinalis involving the sigmoid and descending colon. Dr. J. A. George of Toronto discussed the merits of carotid angiography in localization of supratentorial tumours.

An interesitng family of 79 persons in the easten townships of Quebec, of whom 20 were affected by heart disease, was described by R. G. Fraser of Montreal and his colleagues. The main pathological findings at post-mortem examination were asymmetrical cardiac hypertrophy, patchy myocardial fibrosis and vascular hypoplasia. Dr. S. J. Brown of Montreal



Alex Gray, Toronto

Discussing program highlights at the 23rd annual meeting of the Canadian Association of Radiologists are the newly elected president and vice-president, Dr. A. E. Childe, Associate Professor of Radiology, University of Manitoba, and Dr. D. L. McRae, Radiologist-in-chief, Montreal Neurological Institute.

discussed radiological features in tuberous sclerosis, pointing out that bone changes in this disease are much more common than have been thought, as shown by the high incidence of radiographic changes. In the bones of the hands and feet, these changes are found in about 66% of patients, and in the calvarium in about 40% of patients. Dr. G. O. Sutherland of Toronto described his technique for the examination of the fractured pelvis, by which fracture patterns might be more closely correlated with the type of injury, and the mechanism of injury more clearly demonstrated.

The scientific session continued on Tuesday morning with a paper by Dr. M. F. Bennett and his colleagues from Montreal, on the erect lateral projection of the pelvis as the first procedure in pelvimetry. They were concerned to reduce the dose of radiation given to the pregnant woman, and had found that on the basis of this single film, vaginal delivery was predictable in about 70% of patients examined. The other 30% needed further pelvigraphic study. Dr. A. Jutras of Montreal said that the coupling of the image intensifier and television had created various new remotely operated x-ray techniques. These newer techniques had made elaborate x-ray examinations safe, fast, easy and comparatively economical. For the patient, they meant reduced radiation dosage, more comfort and calm. He discussed recent developments in the field of radiological television. Dr. M. D. Jones of San Francisco described cineradiographic studies of the cervical spine, and Dr. J. S. Dunbar of Montreal reviewed two cases in which an isolated tracheo-œsophageal fistula had been demonstrated by cinefluorography. Dr. J. M. Darte of Toronto discussed his experience with 40 cases of histiocystosis-X and Dr. W. R. Bruce of Toronto described the suppression by cortisone of acute local radiation reaction.

Studies by Dr. E. A. McCulloch of Toronto had shown that the radiation sensitivity of mouse bone marrow cells is similar in magnitude to that reported for human cells in tissue culture and for mouse leukæmia cells. The rotational cobalt 60 therapy unit installed at the Ontario Cancer Institute was described by Dr. J. R. Cunningham of Toronto.

On Tuesday afternoon there was a panel discussion on bone tumours with Dr. L. R. Harnick as moderator and Drs. W. Anderson, F. P. Dewar, W. Allt and R. A. Lobb of Toronto as jury. This was followed by a paper by Dr. G. B. Goodman of Vancouver on cancer of the cervix, with an analysis of series treated by radiotherapy, combined surgery and radiation and surgery alone. The five-year survival rate in the group treated by radiation alone was 51%. Dr. R. L. Duberger of Sherbrooke, Quebec, showed slides illustrating five cases of Milkman's syndrome which had occurred after gastrectomy and Dr. I. Sedlezky of Montreal showed how five tumours of the papilla of Vater, as well as the œdema of the papilla due to a stone, had been demonstrated by careful technique. An evaluation of present methods of study of the gall bladder and the use of intravenous cholangiography was made by Dr. W. A. Shaver of Fergus Falls, Minn.

On Wednesday morning the session began with an analysis by Dr. C. Don of Ottawa of 100 normal intravenous pyelograms to determine the limits of normal variation, and to compare results with the asymmetry of the kidneys found in six cases of unilateral disease of the renal artery. This was followed by a paper on osteomyelitis of the spine by Dr. A. J. Richards of Regina and one on significance of a paravertebral mass in lesions of the spine by Dr. R. K. Merriam of Montreal. Dr. S. P. Traub of Saskatoon discussed the classification, clinical findings and x-ray changes in spinal angiomas, and Dr. R. M. Cunningham of Montreal described his experience of mouth and throat cancer in Burma. Dr. J. C. F. MacDonald of London, Ontario, reviewed the differences in physical characteristics of radon and gold-198, and presented the physical basis of a dosimetry system for the latter. Dr. D. J. Wright of Toronto described physical and clinical experience with the linear accelerator, and Dr. K. G. McNeill of Toronto showed the results of measurement of cæsium activity arising from fall-out, which he had recently made on 50 Toronto residents.

The Gordon Richards Memorial Lecture was given by Dr. Robert S. Stone, professor of radiology, University of California, on "Factors influencing maximum permissible doses of radiation".

At the annual business meeting, the following resolutions were approved: that the Canadian Association of Radiologists appoint a committee to prepare a "Code of practice for the protection of persons exposed to ionizing radiations"; and that the Canadian Association of Radiologists prepare a plan for registering all sources of producing ionizing radiation and invite the federal and provincial governments to undertake this registration.

FIFTEENTH INTERNATIONAL CONFERENCE ON TUBERCULOSIS

The Fifteenth International Conference on Tuberculosis was held in Istanbul, Turkey, September 11-18, 1959, and was attended by some hundreds of delegates representing most of the countries in the world. Whether this conference is held in Copenhagen, Rio, Madrid, New Delhi or Istanbul, it always attracts a considerable attendance, a testimony to the great activity of the International Union against Tuberculosis, and to the growing prestige of this voluntary organization.

Role of the International Union Against Tuberculosis

One may ask whether the role of the International Union against Tuberculosis is likely to diminish in view of the fall in mortality rates from tuberculosis and the temptation in certain well-developed countries to relegate this disease to the rank of less urgent public health problems. However, the contrary is happening and there has never been so much consultation of the Union by so many countries and so much participation in its work.

In order to explain this astonishing paradox, two reasons will suffice:

(a) Antituberculosis work is taking on a new direction, and because of this demanding new studies and an adaptation to new methods. Tuberculosis is not dead, but is still epidemic among immense populations representing at least half of the human race. Moreover, although mortality rates have fallen, biological cure as estimated by the elimination of bacilli from the sick body and not just by clinical symptoms, radiographic signs, and results of bacteriological and pathological tests, is not yet the order of the day. In fact, problems of relapse (in percentages varying from 10 to 30%) and rehabilitation of tuberculous patients are just as acute as in years past. Furthermore, resistance to antibiotics and the existence of atypical forms of mycobacteria have brought new problems. The role of vaccination in the different countries of the world has still to be defined. Methods of case-finding by tuberculin and x-rays have to be thought out afresh. In addition, there are problems of domiciliary treatment, the new role of dispensaries and the use of the empty beds in sanatoria, as well as the integration of official and voluntary organizations against tuberculosis.

(b) As the second reason, I would suggest that tuberculosis is not, so to speak, a medical specialty, but actually involves the whole of medicine, the whole of pathology and the whole of immunity. Discoveries in this field have had and will continue to have profound repercussions on other aspects of medicine and public health. It is possible that this disease will disappear from the earth before its proper biological mechanism is known. However, it is a fascinating study and it is not surprising that physicians and scientists have a great desire to meet on the occasion of international tuberculosis conferences, at which questions with an enormous range are discussed.

Organization of the Conference

The conference took place from September 11-18, under the auspices of the Union, the National Turkish Association Against Tuberculosis and the Faculty of Medicine of the University of Istanbul. The president was Professor Tegsik Saglam and the President of the Turkish Republic was the patron. I would like to pay tribute to the presidency of Professor Saglam and also to the Secretary General of the Committee of Organization, Dr. Ismail Gökçe, who performed a magnificent task of organization under difficult conditions. Istanbul is an ideal city for such a congress. Situated on the

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frontiers of two worlds, this city is very easy of access both from east and west. A city of minarets and of marvelous mosques, of famous ruins, it is a centre for tourists and archeologists. Most of the congress participants took advantage of their presence to visit Greece and on their return Asia Minor and the Near East.

The sessions were held in the big, modern university and the congress participants were scattered around in various hotels, some of which were rather distant. When Istanbul possesses a hotel capable of taking care of such congresses, or at least several hotels near the centre of the congress, it will become the ideal city for these gatherings.

Scientific Program

The scientific program consisted of eight symposia on the following subjects: antituberculous chemoprophylaxis in its clinical, experimental and social aspects; the problem of atypical acid-resistant bacilli; present-day indications for surgical treatment of pulmonary tuberculosis; new drugs; relapse of pulmonary tuberculosis; health education in relation to new treatments; the role of social work in combating tuberculosis; and new features of rehabilitation of the tuberculous. In between these symposia there was a seminar on acquired immunity in tuberculosis. On Saturday, September 19, after the conference, there was another seminar on the role of BCG vaccination in the various countries of the world. This new setting of the congress was very successful but the number of speakers somewhat interfered with the interest of the discussions. It was rather surprising to find that even before the conference the reports had been published in the *Bulletin of the International Union Against Tuberculosis* (Vol. 24, No. 4, July-October 1959). The seminars will be published in full in the near future. Seminars and symposia are valuable techniques provided that most of the shades of opinion are expressed and that discussion is allowed to range freely.

Of the seven sections of the scientific exhibition the one on health education in the service of antituberculosis work was really remarkable. Large panels set forth the 10 rules for combating tuberculosis in the fields of health education, BCG prevention, case finding, treatment and rehabilitation.

Work of the Union Committees

During the congress there were other scientific activities, in particular the meetings of the various committees of the International Union. These nine committees each specialize in a particular aspect of antituberculosis work: epidemiology, BCG, antibiotics and chemotherapy, health education, rehabilitation, radiology and systematic examinations, laboratory methods, surgery of tuberculosis and collapse therapy, ambulatory treatment and domiciliary treatment. They each consist of a president and a dozen experts and have a moderator. In these committees, the scientific policy of the Union is elaborated and the problems submitted by the various countries in the Union are studied.

It is impossible to summarize here the work of each of these committees but I would like to mention, as president of the BCG committee, that during the Istanbul meeting results were announced and discussed of interlaboratory experience in comparison of methods for studying BCG, 15 laboratories from various parts of the world being represented. This bold experiment undertaken by the BCG Committee gave most encouraging results. The committee has discovered a new statistical and biological tool for evaluating methods and comparing different strains of BCG and different vaccines. Perhaps this work may enable us to draw up bases for standardization of BCG vaccine.

Receptions

Several brilliant and most picturesque receptions were offered to the congress participants. One by the Mayor of Istanbul took place at an ancient fort built in the 15th century on the European side of the Bosporus by Sultan Mehnet. This fort commands a magnificent view of the Bosporus and the Asian shore. At the reception, a Turkish military band in ancient costume accompanied a mock sabre battle. Another splendid party was given by the government in the Palace of Dolma Baatche, in a sort of fairyland with enormous candelabras, a "thousand and one nights" feast, during which 2000 guests were given a Turkish supper. The National Turkish Association Against Tuberculosis organized a moonlight outing on the Bosporus and the Marmora. This was an unforgettable spectacle.

The BCG sub-committee met in a sanatorium on the Asian shore of the Sea of Marmora. The hospitality of the director, Dr. Abeit Köymen, and his personnel was of the highest order. The Minister of Labour, Mr. Haluk Saman, also did us the honour of being present at the reception and lunch. As president of the BCG committee I found myself sitting beside him and had the privilege of a long conversation with this remarkable man on the problems of work and health in Turkey and throughout the world. For the ladies, there was a special program of visits to palaces, mosques and museums, with an excursion to the Islands of the Princes.

To sum up, the Istanbul conference did not disappoint the 1200 delegates who attended. The Turks went out of their way to be agreeable and hospitable and to attend to the pleasure and welfare of the congress participants. I met men of the first order there, and I am sure that Turkey is moving forward. Old Istanbul is disappearing to make place for a new and modern city which however will no doubt keep its ancient ruins, its fine monuments and its characteristics of the ancient capital of the world.

By a vote of 45 against 15, Canada was chosen as the site for the 16th Conference of the Union in 1961. Dr. G. J. Wherrett, Secretary of the Canadian Tuberculosis Association, will be president. Toronto will have the honour of being host to the congress but it is probable that either before or after the congress there will be a symposium in Montreal. Canada will find it difficult to rival the other countries which up to now have shared the honour of housing the congress of the International Union Against Tuberculosis. However, Dr. Wherrett can rest assured of the most loyal and complete collaboration from all those working against tuberculosis in the world.

ARMAND FRAPPIER

OBITUARIES

DR. F. R. V. BATESON, 63, died in the Beck Memorial Sanatorium, London, Ont., on November 24. Born in Brougham, Ont., he went to the University of Western Ontario to study medicine. After graduating in 1925, he joined the staff of the Beck Memorial Sanatorium. Later Dr. Bateson entered private practice in Park Hill and subsequently became a member of the staff of the Westminster Hospital in London.

He is survived by his two sons.

DR. MELVILLE MARSHALL BROWN, 51, died in the Winnipeg General Hospital on November 9. A native of Melville, Sask., he received his medical education at the University of Manitoba, where he graduated in 1933. From 1935 to 1940, Dr. Brown practised in Waskada, Man., and then served overseas with the RCAMC during World War II. After the war he returned to Winnipeg and resumed his practice there.

Dr. Brown is survived by his widow, a daughter and a son.

DR. A. L. CALDWELL, 67, of Saskatoon, died suddenly on December 6. He was born in Reston, Man., and received his medical degree at McGill University in 1921. After graduation he began to practise at Empress, Alta., and three years later moved to Evansburg. In 1928 Dr. Caldwell moved to Saskatchewan and during the years of depression and drought he was the only doctor in a territory that extended from Swift Current to Empress. During the Second World War he served in the army as a surgical specialist and on his discharge moved to Saskatoon, where he remained until his death.

His widow and one son survive him.

DR. ALAN H. GREENWOOD, 70, of St. Catharines, Ont., died on November 23 in Boston, where he had been undergoing medical treatment. He attended McGill University for his medical studies and graduated in 1918. During the First World War he served with the RCAMC and then did his postgraduate training at the Montreal General Hospital from 1919 to 1923. Later he returned to St. Catharines and joined his father in practice there. Dr. Greenwood was on the consulting staff of the Hôtel-Dieu and St. Catharines General Hospitals.

He is survived by his two sons, one of whom is Dr. F. Greenwood of Montreal.

DR. GEORGE C. LECKIE, 61, died at his home in Sarnia, Ont., on November 21. A native of Sarnia, he took his degree in medicine at the University of Western Ontario in 1923. After graduation he went to New York, where he took a six months' postgraduate course at the New York Lying-In Hospital and the Babies' Hospital. In 1924 Dr. Leckie went into partnership with another doctor in Detroit for five years and then went to the University of Pennsylvania in 1930 for a two-year postgraduate course in urology. After qualifying as a specialist in urology, he returned to Detroit and practised there until his retirement in 1956, when he returned to live in Sarnia.

PROVINCIAL NEWS

ALBERTA

The third of this winter's postgraduate courses for general practitioners was held in Edmonton on January 18 and 19. These courses are conducted by the C.M.A., Alberta Division, and the Faculty of Medicine, University of Alberta. This third course was on obstetrics and gynæcology and the guest speaker was Dr. Brian B. Best, associate professor of obstetrics and gynæcology, University of Manitoba. Previous courses were in: Hæmatology: guest speaker, Dr. Douglas G. Cameron, professor of medicine, McGill University; and Recent advances in surgery: guest speaker, Dr. Allan D. McKenzie, professor of surgery, University of British Columbia.

The Government of Alberta has announced plans for the training of a new group of health personnel to be known as registered dental auxiliaries. This move results from the urgent need for dental care that exists in Alberta and which has been under discussion by representatives of the Department of Health of the Province, the University, the Faculty of Dentistry, and the Alberta Dental Association.

Under the plan, young men and women of grade XII standing will take a two-year course at the University of Alberta. This will prepare them to be competent auxiliary personnel who will assist the dentists in preventive dental care throughout the province. Financial assistance for those requiring it will be obtainable through the Alberta Government Queen Elizabeth Scholarship Fund.

Plans at present call for progressive screening of preschool and school-age children up to the age of 12 years. Dental needs will be noted, cavities filled, necessary extractions made, teeth cleaned and treated with topical fluorides and advice given on the protection of the teeth. In this work, the dental auxiliaries will act as dentists' assistants and initially will probably be limited to putting fillings in cavities which the dentist has prepared, and cleaning the teeth and applying local fluorides. They will work only within the framework of the provincial health units and under the supervision of a qualified dentist. Plans at present indicate that after three years in the field a registered dental auxiliary will be able to return to the University and qualify in dentistry.

Until the proposed plan goes into effect arrangements are being made to utilize the services of students who have completed their third year in dentistry. These would go out into the rural areas and carry out preventive services as outlined above. A large number of the members of the Alberta Dental Society have already indicated their willingness to assist the program by leaving their own practices for two or more weeks each year to go to outlying areas to man the portable dental clinics along with the third-year students. The provincial government will cover the costs of preventive work on children only. Possibly, if time permits, necessary work could be carried out on adults at the patient's own expense. The Government points out that the proposed service will not be a program of socialized dental care.

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As a result of the recent balloting, the following members have been elected to the Council of the College of Physicians and Surgeons, Province of Alberta: Medicine Hat District, Dr. B. M. MacLeod; Calgary District, Dr. J. R. Ibberson; Red Deer District, Dr. G. E. Foster; Edmonton District, Dr. Lloyd Grisdale; Northern Alberta District, Dr. J. B. T. Wood.

The term of service is two years, the elections being staggered in the various districts to give continuity of Council.

On October 12 and 13, 1959, the sixth annual short course in clinical medicine for podiatrists was held at the University of Alberta. This course is arranged by the department of extension, University of Alberta, in co-operation with the Alberta Podiatry Association, and is open to all practising podiatrists in Canada. This course is not under the ægis of the Faculty of Medicine though members of that faculty are on the program. The attendance at this course was eight podiatrists.

There was excellent attendance at the early winter meeting of the Alberta Thoracic Society held in Red Deer in November. Papers presented were: "Open heart surgery"—Dr. John C. Calaghan, Edmonton; "The management of penetrating wounds of the chest"—Dr. C. M. Couves, Edmonton; "Staphylococcal pneumonia"—Dr. George E. Miller, Calgary; and "The present status of the tuberculosis problem in Alberta"—Dr. G. R. Davison, Edmonton.

The thanks of the organization were extended to the Alberta Tuberculosis Association, who arranged a dinner as their contribution toward this professional educational effort.

The Alberta branch of the Eye Bank of Canada was recently established at the University of Alberta. This is the fifth such branch in Canada.

Tenders are now being called for the new nine-million-dollar Royal Alexandra Hospital in Edmonton. Bids are to be on straight tender or, a new procedure, under lease-back arrangement on a 25-year basis.

Work is nearly completed on the new 2.7-million-dollar nurses' residence and training school at the same hospital. It is expected that this unit will be open in the spring.

As part of its five-year program, the Alberta Government has announced the provision of grants for the acquisition of recreational facilities by communities of one hundred or more population, exclusive of Calgary or Edmonton. Grants will be on the basis of $10 per capita and will apply to any feasible plan of recreation facilities and to any project undertaken since January 1959 or which can be proceeded with during the subsequent five years. Consideration will be given to projects planned jointly by adjoining communities. The plan does not affect in any way the existing government assistance of $7000 towards erection of swimming pools in towns and villages.

W. B. PARSONS

SASKATCHEWAN

The final report of Dr. W. P. Thompson, retiring President of the University of Saskatchewan, indicated that the University Governors would soon have to make important decisions regarding the University's extension work and its public service endeavours.

Student enrolment will be limited after 1964, and this will in all likelihood coincide with the expansion of Regina College. There are now more than 4000 students at the University in Saskatoon and in five years an enrolment of 7000 to 8000 is anticipated.

Dr. Thompson also reported that the University Board of Governors has decided not to establish a veterinary college in Saskatoon.

Total registration for all types of classes offered in 1959-1960 at the University of Saskatchewan was 10,703. This figure includes degree students at Saskatoon and Regina, enrolment in junior colleges (Campion, Luther and St. Peter's); enrolment in the school of nursing, agriculture, summer school, intersession classes and correspondence and evening courses.

A guaranteed 40-hour work week, higher minimum wage and a medical-care plan were among items requested by the Saskatchewan Federation of Labour during November in its annual brief to the Provincial Cabinet in Regina.

Dr. M. H. Brook of Saskatoon recently gave a paper on "Direct artificial respiration—training program using the Brook airway" at a meeting of the Royal Society of Medicine in London, England, during December. He was also invited to participate in a symposium on artificial respiration at a meeting of the Allied Services Division and of Anæsthesiologists.

In a recent speech delivered at North Battleford, Mr. Ross Thatcher stated that the Liberals would continue the Saskatchewan Hospital Insurance Plan. They would not, however, embark on socialized medicine. Under the Liberal plan, one of the voluntary plans which now covers a total of one-third of the province's population, he stated, would be extended to all persons in the province, but only after the people had been told what it would cost, and had a chance to vote on it.

During December, the Hon. T. C. Douglas made a public broadcast on "Prepaid medical care" in which he announced a plan which his government believes to be sound, to provide prepaid medical care for the residents of Saskatchewan.

In setting up such a plan, he pointed out a number of basic principles which his government felt necessary. The first was the prepayment principle in order that the costs would be spread over the entire population instead of being borne, "as they are now, by those who are unfortunate enough to be ill".

The second principle was that a medical-care program must have universal coverage so that every person in the province would be covered.

The third principle was that there must be a high quality of service and the plan must permit the integration of curative and preventive services.

The fourth principle was that it must be a government-sponsored program administered by a public body responsible to the Legislature and through it to

the entire population, with part of the cost borne out of general revenue, thereby keeping the per capita tax at a figure which every family in the province could afford to pay.

The fifth principle was that the plan would be established in a form that is acceptable both to those providing the service and to those receiving it.

Mr. Douglas also announced that it was the intention of the government to appoint an Advisory Committee on Medical Care. This body would be comprised of three persons named by the medical profession, three representatives of the government, three representatives of the general public and one appointee from the University of Saskatchewan College of Medicine.

The committee would be provided with an adequate secretariat and they would be asked to recommend to the government the best methods of developing a medical-care program in keeping with the basic principles outlined. Mr. Douglas announced also his expectation that the committee would be able to submit their final report during the latter part of 1960 and that the province-wide medical-care program could be started in 1961.

Mr. Douglas also stated, "If we can do this—and I feel sure we can—then I would like to hazard the prophecy that before 1970 almost every province in Canada will have followed the lead of Saskatchewan and we shall have a national health insurance program from the Atlantic to the Pacific."

G. W. PEACOCK

MANITOBA

The obstetrical and gynæcological department of St. Boniface Hospital staged a symposium on maternal mortality on December 5, with Dr. John L. McKelvey, professor of obstetrics and gynæcology, University of Minnesota, and a former Canadian, as guest speaker. Professor Elinor Black presided at the morning session when case histories of maternal deaths from the Brandon General, Misericordia, Grace, St. Boniface and Winnipeg General hospitals were presented. Dr. McKelvey commented on each. Dr. James R. Mitchell showed with graphs how the present maternal mortality rate was one-tenth of what it was 25 years ago and one-half of the 1949 rate. At present, hæmorrhage, toxæmia and infection (in that order) are the chief causes of maternal deaths. Dr. Ross Willows presided after a luncheon served in the hospital. Dr. McKelvey said that the death of any woman who was pregnant or had recently been delivered should be considered as a maternal death. He spoke of the measures used in Minnesota to collect and evaluate all such maternal deaths from the standpoint of preventability. Largely as a result of the program initiated by Dr. McKelvey, Minnesota now has the second lowest maternal mortality rate in the United States. The symposium was well attended and it provided five hours' credit for the College of General Practice.

The provincial government has signed an agreement with federal authorities to bring nursing stations operated by the Indian Health Services under the Manitoba Hospital Services Plan. They are at Indian reservations at Cross Lake, God's Lake, Island Lake, Gypsumville, Nelson House, Oxford House, Ste-Thérèse's Point, Split Lake and Little Grand Rapids. A hospital at Berens River operated by the Grey Nuns is also included.

Each of the nursing stations is staffed by two registered nurses who use radio telephone to keep in touch with doctors in Norway House, The Pas and Pine Falls.

Dr. K. I. Johnson of Pine Falls has been appointed to a three-year term on the Hospital Advisory Commission, succeeding Dr. J. E. Hudson of Hamiota.

Dr. R. G. Handford has opened an office at 605 Medical Arts Building, Winnipeg, for the practice of internal medicine.

The Market-Opinion Research Company of Detroit has submitted a report to the Manitoba Health Service, formerly Manitoba Medical Services, on the attitudes of the Winnipeg public to medical care coverage. About seven out of ten Winnipeg families have medical coverage and of these, more than six out of the seven carry it with M.H.S. The majority of those having coverage with M.H.S. favour the present (doctor-controlled) type of operation although a considerable number preferred government sponsorship. The most important additional benefit requested was dental care, but of those requesting additional benefits the typical additional amount they were willing to pay was $1.50. Seventy-two per cent of M.H.S. subscribers belong to the group earning over $3000 a year.

Fifteen Winnipeg doctors are now using hypnotism as a useful medical aid for certain patients. They are using it in psychiatry, surgery, obstetrics, ophthalmology, general practice, otolaryngology and anæsthesia. They meet at regular intervals to discuss its application but they warn that not all patients can benefit by its use and that it is not a stage show. Recently one of their number gave an interesting talk before the Medical History section of the Winnipeg Medical Society on the history and nature of hypnotism.

ROSS MITCHELL

ONTARIO

Dr. P. K. Basu has been appointed the Stapells Director of Ophthalmic Research in the University of Toronto. This appointment has been made possible through the generosity of Mr. H. G. Stapells, Q.C., of Toronto. The object of the Stapells fund is to further ophthalmic research work in the department of ophthalmology in the University of Toronto. Dr. Basu will direct and co-ordinate the ophthalmic research in the department of ophthalmology and carry on active research himself towards the prevention and treatment of diseases of the eye.

PRINCE EDWARD ISLAND

The guest speaker at the extramural lecture on Wednesday, December 9, at the Charlottetown Hotel was Dr. J. C. Sinnott, internist of Charlottetown, who spoke on the control of pulmonary ventilation.

Dr. Heinrich Fuerst, a graduate of the University of Munich, has joined the staff of the Riverside Hospital as staff psychiatrist and is now in charge of the Mental Health Clinic for adults. J. A. MCMILLAN

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ABSTRACTS *from current literature*

MEDICINE

The Prominent R-Wave in aVR and V_1 in the Electrocardiograms of Patients with Chest Pathology.

T. T. Fox *et al.*: *Sea View Hosp. Bull.*, 17: 69, 1959.

A prominent R-wave in either aVR or V_1 or in both aVR and V_1 is not an infrequent finding in cases of pulmonary or mediastinal pathology without any evidence of heart disease. A number of illustrations are presented to emphasize the importance of considering extra-cardiac factors in the causation of the R-aVR, V_1 phenomenon. The writers' observations lead them to believe that it is the position of the heart within the thorax that determines the configuration of the QRS complex in aVR and V_1. A subdiaphragmatic process by displacing the diaphragm and mediastinal contents might occasionally be the cause of the pattern under consideration. They suggest that assistance in the interpretation of the electrocardiogram might be derived from careful inspection of the architecture of the atrial complexes, since abnormal atrial complexes are frequently seen in mediastinal shift and rotation.

It is their opinion that alertness on the part of the physician to the possibility of extracardiac factors causing electrocardiographic changes might help to diminish the incidence of iatrogenic heart disease.

S. J. SHANE

Lactic Dehydrogenase Versus Glutamic Oxalacetic Acid Transaminase as Diagnostic Test for Myocardial Infarction.

I. FREEMAN *et al.*: *Am. J. M. Sc.*, 237: 768, 1959.

Simultaneous determinations of the levels of serum glutamic oxalacetic acid transaminase and serum lactic dehydrogenase were made on 60 patients between 12 and 48 hours after the onset of the initial symptoms of acute myocardial infarction. Classical histories of infarction plus serial electrocardiographic changes or necropsy evidence verified the presence of such lesions. All the patients exhibited elevated levels of transaminase, whereas only 35 of the 60 patients had elevated levels of lactic dehydrogenase. If a single test were to be employed to confirm an impression of acute myocardial infarction between 12 and 48 hours of its occurrence, the assay of transaminase would thus appear to be significantly superior to that of lactic dehydrogenase.

S. J. SHANE

Stimulation of Hæmopoiesis by Batyl Alcohol.

J. W. LINMAN *et al.*: *J. Lab. & Clin. Med.*, 54: 335, 1959.

Batyl alcohol is the monoglycerol ether of n-octadecyl alcohol and has been known since 1949 to be capable of stimulating erythropoiesis in rats and in normal human subjects. The authors describe their methods of studying the effect of batyl alcohol on ten normal rats and on four rats conditioned by starvation and hypophysectomy. In the latter group, following three daily 25 mg. injections of batyl alcohol, iron 59 was given intravenously and the uptake of iron 59 in the circulating erythrocytes was determined 24 hours later. Marrow cultures were also evaluated for uptake of iron 59.

Oral administration of batyl alcohol in normal rats results in a striking increase of circulating erythrocytes, reticulocytes, thrombocytes, and leukocytes. There was no increase in hæmoglobin value nor did the hæmocrit value show any important change. The elevated values dropped sharply after discontinuation of treatment. In the starved and hypophysectomized rats, batyl alcohol failed to enhance the uptake of iron 59 or the incorporation of iron 59 into the hæmoglobin. This effect of batyl alcohol is similar to that of the erythropoietic factor of plasma and it is recalled that there is a chemical similarity between batyl alcohol and the thermostable, ether-soluble, plasma erythropoietic factor. The authors discuss the importance of these findings in the elucidation of the mechanisms of erythropoiesis in hæmolysis, following acute hæmorrhage, and in polycythæmia vera. Their findings support the theory that all aspects of hæmopoiesis are under humoral regulatory control.

W. GROBIN

Effects of Certain Pure Long Chain Polyunsaturated Fatty Acid Esters on the Blood Lipids of Man. Preliminary Studies on the Use of Polyunsaturated Fatty Acids in Atherosclerosis.

H. E. WORNE AND L. W. SMITH: *Am. J. M. Sc.*, 237: 710, 1959.

Statistical analysis of the findings of the effects of the various polyunsaturated fatty acids shows a significant correlation between the number of double bonds in the fatty acid molecule and the level of the blood lipids. Four grams per day of the 4-, 5- and 6-double-bonded fatty acids produced significant blood lipid changes reflected by reduced cholesterol levels and a more favourable cholesterol-prolonged ratio. In addition to the cholesterol reduction, a concomitant improvement in the phospholipid levels was noted at this dosage level. An increase in double bonds thus reduces significantly the total quantity of unsaturated fatty acids necessary to accomplish the desired reduction of abnormal lipid levels.

In 88% of the cases exhibiting signs of angina, intermittent claudication or other signs of arterial insufficiency, there was objective evidence of gradual clinical improvement as the blood lipids were reduced to normal levels. In several patients with skin xanthomata, elimination of these lipid lesions was observed to be concurrent with reduction of the accompanying hyperlipæmia or hypercholesterolæmia. Most of the patients reported an increased feeling of well-being coupled with improved cerebration.

S. J. SHANE

Idiopathic Cardiac Hypertrophy with Endomyocardial Fibrosis.

P. J. MCNAMARA, W. H. JACOBS AND R. J. JAFFE: *Ann. Int. Med.*, 50: 1035, 1959.

A case is reported of idiopathic cardiac hypertrophy, initially without any cardiovascular abnormality. When first examined in 1953, because of a purulent lung abscess, the patient had no signs or symptoms of organic cardiac disease and cardiac enlargement was not detected by roentgenogram. When the patient was re-examined 15 months later because of a history of four days of dyspnœa, orthopnœa and pain in the right upper quadrant, his heart was found to be enlarged and a gallop rhythm was noted. The response to digitalis and diuretic therapy was prompt.

Extensive studies revealed no cause for his cardiac disease. He was kept under observation for a period of 33 months. During this period he suffered from cardiac decompensation until the time of his death, which was caused by myocardial failure, recurrent pulmonary infarctions and secondary cor pulmonale.

At necropsy all the cardiac chambers were enlarged. The endocardium was diffusely thickened. No valvular deformities were noted and the coronary vessels showed the usual distribution and were patent. Microscopic examination demonstrated that the endocardium was thickened by dense fibrous tissue, with many areas of infiltration by lymphocytes and polymorphonuclear leukocytes. Many microscopic foci of myocardial necrosis were found.

A review of the literature reveals that this disease is common in Africa. Congestive heart failure with a low pulse pressure results in a similar condition to that noted in constrictive pericarditis, but the presenting findings of cardiomegaly and gallop rhythm are distinctive. Large doses of digitalis were used in this patient without the production of digitalis intoxication. This seems to indicate a loss of sensitivity of the heart to digitalis in this illness, in contrast to the situation in various types of myocarditis. S. J. SHANE

Comparison of the Granuloma-Producing Capacity of Normals and Sarcoid Granuloma Patients: Experimental Analysis of the Sarcoid Diathesis Theory.

H. J. HURLEY AND W. B. SHELLEY: *Am. J. M. Sc.*, 237: 685, 1959.

In an attempt to evaluate the significance of the theory of the sarcoid diathesis in the production of sarcoid granulomas, the granuloma-producing capacity of 300 normal male subjects was compared with that of 35 patients with sarcoidosis and six patients with granulomas from zirconium deodorant. The stimuli employed were sodium stearate, beryllium, silicon, zirconium, and other elements, as well as homologous whole blood. Intradermal skin test injections of all these substances were given and compared clinically and histologically.

There was no significant variation, qualitatively or quantitatively, between the 300 normal subjects and the patients with sarcoidosis or with granulomas from zirconium deodorant to any of the stimuli employed. As a result of these studies the writers doubt that the sarcoid mode of reaction is operative. They consider that a specific granulomagenic substance is responsible for the production of this unusual tissue response and that continued search for such specific granulomagenic substances is indicated. S. J. SHANE

The Postmitral Commissurotomy Syndrome: A Four-Year Clinical, Pathological and Serological Study, and its Relation to Restenosis.

P. LISAN, A. REALE AND W. LIKOFF: *Ann. Int. Med.*, 50: 1352, 1959.

The postcommissurotomy syndrome is a clinical entity probably unrelated to the rheumatic state or its reactivation. It is a benign disease state, producing fever and vague generalized myalgia with chest pains, and is not a factor in causing restenosis of the mitral valve. No mortality or permanent damage results from this syndrome, as would be expected in rheumatic pancarditis. There are no alterations in the ausculfatory findings of the heart and there is no significant change in the heart size. The laboratory studies including serological tests are not compatible with the diagnosis of acute rheumatic state. Finally, as the present evidence suggests, the failure to detect restenosis of the mitral valve over a four-year period in those patients who suffered from postmitral commissurotomy syndrome strongly supports the view that this clinical syndrome is not an expression of rheumatic activity. In most cases, the biopsies of atrial appendage revealed evidence of chronic non-specific carditis with no stigmata of rheumatic disease past or present, while an insignificant number revealed old, burned-out rheumatic carditis. None of the biopsies was pathognomonic of the acute active rheumatic state.

In the present investigation it was not possible to identify a causative agent. The etiology of the postmitral commissurotomy syndrome remains obscure. Therapy was best accomplished by symptomatic treatment, with no greater benefit being obtained by using steroids than that obtained from analgesics given in small doses. The rheumatic state does not usually respond so promptly or completely as does this syndrome.

S. J. SHANE

SURGERY

Experience with Gastric Resection by the Péan-Rydygier-Billroth I Method.

E. POLAK AND V. VOJTISEK: *Ann. Surg.*, 149: 475, 1959.

The end-to-end anastomosis following gastrectomy was first done on dogs by an unknown Philadelphian doctor in 1810. The French surgeon Péan in 1879, and the Polish surgeon Rydygier in 1880, unsuccessfully resected the human pylorus. Billroth was the first to have success in 1881, for his patient lived several months after the operation for cancer of the stomach. Rydygier had lasting success with the operation for stenosis due to ulcer the same year. Other experimenters were concerned in the development of this operation and the originator is difficult to name, though Billroth was the first to use it with survival. Rydygier, and Jedlicka of Czechoslovakia, were the first to use it for ulcer and they defended the procedure. These pioneers all used the lesser curve of the gastric stump for the gastro-duodenal anastomosis, closing the greater curve.

The Billroth II method is used mostly because surgeons learned it from their teachers. The end-to-end operation may be followed by slowed emptying for a while, but this subsides and with the same gastric resection there is better weight gain. The dumping syndrome is more serious and is more frequent after Billroth II.

A study of patients who have undergone the Péan-Rydygier operation at a surgical clinic in Prague, showed 0.65% recurrent ulceration; after the Billroth II there were 0.4% recurrences, and after gastroenterostomy the rate was 5.3%. Re-operation was much simpler with the end-to-end anastomosis.

Contraindications to the Péan-Rydygier resection are the deep penetrating posterior wall ulcer that marks the duodenal stump unsuitable for anastomosis, and the high gastric ulcer with fixed cardia and duodenum making suture without tension impossible. But between 78 and 90% operability for ulcer by the Péan-Rydygier method is achieved at this Czech clinic, depending on the experience of the surgeon, with an over-all mortality of 1.9% including perforations, massive hæmorrhage and recurrent ulcer.

BURNS PLEWES

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Ileocystoplasty. Experimental Studies on Electrolyte Behaviour.

W. K. KERR, A. G. KERESTECI AND V. N. KYLE: *Canad. J. Surg.*, 3: 35, 1959.

The main purpose of the experimental study described here is to trace changes in urine injected into an isolated intestinal loop. Blind ileal loops were isolated in dogs, urine or appropriate solutions were instilled into the blind loops with a syringe and catheter, and the catheter was left in place and the solutions were recovered 60 minutes later. The fate of the urine depended upon its specific gravity (SG); urine of low SG was reabsorbed; that of high SG was diluted by secretions of the intestinal mucosa. Absorption of sodium and chloride varied according to their concentrations in the urine, provided the SG was fixed, but absorption was greatly modified by changes in the latter. For the same concentrations of sodium and chloride, high SG urine showed much less absorption than low SG urine. The ileum reabsorbed more chloride than sodium at all concentrations and regardless of SG. Potassium and urea were both reabsorbed in linear relations to their concentration, and in greater amount from low SG urine.

There is obviously a two-way movement of ions and water across the intestinal mucosa, and results are similar to those in reported experiments on the colon, except that potassium is reabsorbed by the ileum.

The pathogenesis of acidosis due to hyperchloræmia when ileum is used to replace ureter, is similar to that in uretero-colic anastomosis. Dehydration caused by excess sodium and chloride and urea gives rise to acidosis; this tendency is increased by the excess absorption of chloride. Lack of potassium is secondary to the dehydration and acidosis.

When a loop of ileum is used to replace a portion of the urinary tract, the electrolytic imbalance should be combated by administering large amounts of fluid poor in salt; in severe cases, sodium and potassium as citrate or carbonate should be given by mouth.

Causes and Prevention of Œdema of the Arm After Radical Mastectomy.

J. P. WEST AND J. B. ELLISON: *Surg. Gynec. & Obst.*, 109: 359, 1959.

Œdema of the arm is a common and occasionally a distressing complication of radical mastectomy. Approximately 50% of patients have some postoperative œdema of the arm, but in only 5 to 10% is this of a marked degree.

It appears that lymphatic obstruction is the most important cause of œdema, but venous obstruction can also produce œdema and occasionally be the more important factor. Venograms are useful in demonstrating the presence or absence of such obstruction. Significant œdema of the arm was uncommon in the uncomplicated case. Delayed wound healing, infection and the prolonged collection of fluid in the axilla appeared to be the most important causes in the cases reviewed.

Radiation therapy was considered to be only a minor causative factor. The type of incision, provided primary healing occurred, appeared to be of little importance. The report does not consider the effect of the extent of axillary or supraclavicular metastases, or the value of lymphangiography. JOHN A. PALMER

The Lymphatics of the Breast.

R. T. TURNER-WARWICK: *Brit. J. Surg.*, 46: 574, 1959.

The lymphatics of the breast were studied by the preoperative injection of patent blue or iron dextran so that the vessels could be seen at the radical mastectomy, or by injecting radio-active gold and taking autoradiographs of the surgical specimen. The Au^{198} method is most accurate. The trunk lymphatics accompany the blood supply. The internal mammary chain is an important pathway, draining lymph from both the lateral halves of the breast, but there is no significant drainage to contralateral nodes. In a small proportion of patients, the posterior intercostal lymph node received breast lymph. The so-called subareolar plexus played no important role in pathways of lymph drainage, nor do the minute lymphatics of the deep fascia. BURNS PLEWES

Results of Treatment of Papillary Carcinoma of the Thyroid.

G. CRILE, JR., J. M. MCNAMARA AND J. B. HAGARD: *Surg. Gynec & Obst.*, 109: 315, 1959.

In 1955, Crile, Suhrer and Hagard reported the results of "conservative" surgical treatment of 107 patients with papillary carcinoma of the thyroid. It was felt by the authors that the term "conservative" had been misconstrued to mean incomplete excision of the primary or simple enucleation of the involved nodes. This report points out that the term "conservative" applies not to the removal of the primary tumour or its metastases, but to the conservation of uninvolved muscles, vessels and nerves.

The operation required in the individual case depends on the extent of the disease, but should always include the wide resection of the primary tumour. If the cancer is localized to a single lobe of the thyroid, complete removal of that lobe, sometimes with the isthmus and a part of the contralateral lobe, is all that is necessary. In none of the 75 such patients in this series has cancer appeared in the contralateral lobe.

If the regional lymph nodes are explored and there is no gross evidence of metastasis, there is no necessity for prophylactic dissection of the neck. In only one of 25 such patients did cervical metastases develop at a later date. When lymph nodes are involved, the operation should include removal within their enveloping fat of lateral cervical, paratracheal, superior mediastinal and midline laryngeal nodes. These can usually be removed *en bloc*, but sacrifice of the sternomastoid muscles and nerves is rarely necessary.

The five-year-survival rate of 88 patients was 94%, despite the fact that 75% of the cancers had metastasized at the time of operation. If patients live five years without evidence of recurrence, subsequent evidence of disease is rare.

The authors believe that one of the factors contributing to the high survival rate in this series is the exclusion of papillary carcinomas containing areas of anaplasia. These tumours behave as anaplastic carcinomas and should be considered and treated as such.

The other factor of importance is the routine postoperative use of desiccated thyroid, two or preferably three grains daily. Its use has a definite restraining effect on the growth of residual cancer.

JOHN A. PALMER

THERAPEUTICS

Septic Arthritis: Its Relation to Intra-Articular Injections of Hydrocortisone Acetate.

J. D. C. GOWANS AND P. A. GRANIERI: *New England J. Med.*, 261: 502, 1959.

The intra-articular injection of hydrocortisone, while not a curative procedure, has proven itself a useful adjunct in the treatment of painful joint conditions. It is a therapeutic measure which is not without danger of complications and should be employed only after careful study of the individual case. Infection may be introduced into the joint with the injection. Joints may be injected which are the site of unsuspected sepsis. The authors present cases and suggest a third complication, namely, that the presence of hydrocortisone in the joint so lowers local resistance as to favour the setting up of joint sepsis from organisms circulating in the blood. Intra-articular injections of hydrocortisone should be used only after careful exclusion of infection within the joint, and a rigidly aseptic technique should be employed.

NORMAN S. SKINNER

Current Status of Therapy in Glomerulonephritis.

L. A. RANTZ: *J. A. M. A.*, 170: 948, 1959.

While post-streptococcal nephritis has a striking tendency to recovery, other types of nephritis usually have a protracted course. It is essential to establish an etiological diagnosis before attempting treatment. Culture of the nasopharynx and the determination of the serum antistreptolysin O titre will help decide whether or not the disease is due to streptococci.

Penicillin in one single large dose, or repeated doses over two weeks, should be administered during the acute episode, and it may be desirable to protect these patients against subsequent group A hæmolytic infections by continuous administration of penicillin for six months. This can be done either by injecting 1,200,000 units of benzathine penicillin G intramuscularly at monthly intervals or by oral therapy. The latter is not recommended because it is less reliable. Restriction of activity should be enforced, both during the initial stage and later, in the hope that chronicity may be prevented. Patients with œdema and oliguria should have restriction of fluids to 700 c.c. over the combined urinary output and vomitus, and of sodium to 300 mg./day. The diet should be high in carbohydrate and low in potassium. After the œdema has been cleared and the blood pressure returned to normal, the diet may be liberal and fluids unrestricted. In prolonged oliguria, an effort to reduce the total body store of potassium should be made by administration of an ammonium carboxylic ion exchange resin in doses of 50 g. daily.

Congestive heart failure is treated with digitalis while diuretics are contraindicated. In severe cases, phlebotomy may be required. For convulsions parenteral magnesium sulfate, as used in the past, is hazardous; the newer antihypertensive drugs, such as hydralazine hydrochloride and reserpine (in combination), are effective and non-toxic. They have to be used carefully in chronic nephritis and only in those cases where rapid deterioration of eyes, heart or renal function related to hypertension is taking place. The use of blood for correction of anæmia of chronic renal failure is hazardous and contraindicated. W. GROBIN

Steroid Therapy in Endocrine Disorders.

J. E. HOWARD: *J. A. M. A.*, 170: 952, 1959.

In adrenal cortical hypofunction (Addison's disease), 2 mg. of desoxycorticosterone acetate daily intramuscularly and 12.5 mg. of cortisone orally after breakfast and supper will restore the patient to near normal within one to two weeks. The attempt to treat the patient with cortisone alone in doses of 50 or even 75 mg. has resulted in symptoms of hyperadrenocorticism, perhaps because patients with endocrine deficiencies are sensitive to the hormone in which they are deficient. Good results can be obtained with injections of desoxycorticosterone acetate which may be given once a month intramuscularly in a dose of 60 mg. During periods of stress, patients with Addison's disease should be given 50 to 100 mg. of cortisone a day. In acute crises of adrenal insufficiency, as much as 300 mg. or more of hydrocortisone may be needed in 24 hours. In pituitary insufficiency, the adrenal cortical replacement is almost identical with that in primary adrenal insufficiency, except that under most conditions there is no need for sodium-retaining hormone.

Before removing a tumour for adrenal cortical hyperfunction (Cushing's syndrome), 100 mg. of cortisone per day is given i.m. for two or three days and this procedure is carried on for four days postoperatively. Usually these patients require more than the average replacement dose after adrenalectomy, and only rarely can they be controlled with less than 50 mg. of cortisone per day.

In pituitary disease causing hypothyroidism, as well as adrenal atrophy, the administration of thyroid hormone may produce an adrenal crisis, and it is a good precaution to provide replacement of corticosteroid to severely myxœdematous persons when thyroid therapy is started.

(This paper was one of a symposium and panel discussion on "Use and abuse of adrenal steroids", and in an introduction by the chairman-moderator of the program, T. M. Brown, the dangers of adrenal steroid therapy were outlined.) W. GROBIN

Gastro-intestinal Bleeding during Tolbutamide Therapy.

M. L. GELFAND: *J. A. M. A.*, 171: 258, 1959.

Two cases of upper gastro-intestinal bleeding in diabetics receiving tolbutamide are reported. A 59-year-old man and a 72-year-old woman had been receiving tolbutamide for over six months, and both were admitted to hospital with severe anæmia and tarry stools of several days' duration. The man was found eventually to have a deformed duodenal cap, compatible with the diagnosis of chronic duodenal ulcer, and the woman had a history suggestive of an ulcer for many years without, however, such a lesion's ever being demonstrated.

The author comments on the possibility that these cases represent gastro-intestinal hæmorrhage following tolbutamide—similar to that following administration of other drugs (phenylbutazone, steroids, and salicylates). He also mentions having encountered a case of leukopenia with a purpuric skin rash after use of tolbutamide. Some caution in administering tolbutamide to patients with a known history of gastro-intestinal symptoms is indicated. W. GROBIN

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BOOK REVIEWS

CANADIAN CANCER CONFERENCE. Edited by R. W. Begg, University of Saskatchewan, Saskatoon. 461 pp. Academic Press Inc., New York, 1959. $12.00.

In his foreword, Professor H. E. Rawlinson draws attention to the two preceding conferences, the first dealing with experimental tumours, tumour-host relations, enzymes, and ionizing radiation and the second with the cell, leukæmia and chemotherapy, hormones and cancer, immunity and basic mechanisms. The present report carries this plan further and deals with nucleic acids, genetics, viruses and tumours, and the biology of cancer.

Here is presented the work done by Canadian scientists and the progress which they have accomplished in unravelling the biological problems of cancer. The present volume is complementary to its predecessors and rounds out the full field of research endeavour.

All Canadians will feel very proud in realizing the high standard of work which is being carried out in the research laboratories of this country with the support of the National Cancer Institute. The conferences have not only provided an opportunity for the scientist to meet and exchange ideas but in the published transactions present a mass of material dealing with each phase of the research of cancer.

In addition to the presentations of Canadian scientists, outstanding authorities have come to the conferences and given reports on their work and appreciations of the present status of controversial subjects. To this volume twenty-five scientists from the U.S.A., the United Kingdom, Europe and Australia have made contributions. Sarah Stewart of Bethesda presents her epoch-making report on the polyoma virus, L. H. Gray of England discusses the importance of oxygen tension as a radiation-sensitizing agent, and in answer to the virologists, Burnet of Australia reviews the evidence of carcinogenesis from the basis of somatic mutation.

Once again R. W. Begg has compiled a report which will be of great interest to all who are working in cancer research. For those whose interest is impersonal it records slow but steady progress in cancer research which every year brings the answer inevitably nearer.

SMOKING. The Cancer Controversy. Sir Ronald A. Fisher. 47 pp. Oliver and Boyd, Edinburgh and London; Clarke, Irwin and Company Limited, Toronto, 1959. $0.55.

Sir Ronald Fisher has brought together here his recent lectures and letters, published in various journals, on the pulmonary cancer and cigarette controversy, a further argument regarding inhaling, and also a lecture on "The Nature of Probability" for a non-mathematical audience.

Seldom having the time to acquaint ourselves thoroughly with all the evidence on any subject, weigh it critically and draw such deductions as it demands, we are all inclined to accept what we find in the briefest summaries in medical journals, or in the persistent propaganda in the lay press, the radio or television. A first-class antidote to this unfortunate but largely inevitable intake of questionable stuff from many sources is provided by this collection from a mastermind.

Sir Ronald exposes serious holes in the evidence that cigarette smoking is an important cause of lung cancer and suggests practical ways of getting further evidence that should definitely confirm or confute that contention. Important as are Sir Ronald's findings on any question, it is not these alone that make this pamphlet a most valuable one; equally valuable, or more so, is the example he sets in the way he argues, logically and carefully, and sets forth his argument simply but pointedly so as to make fascinating reading. This is a timely collection deserving to be read, and with profit, throughout all of medicine.

MAJOR ENDOCRINE DISORDERS. S. Leonard Simpson, Consultant Endocrinologist, St. Mary's Hospital, London, England. 459 pp. Illust. 3rd ed. Oxford University Press, London and Toronto, 1959. $7.50.

Endocrinology is now an integral part of general medicine, and every internist in addition to being on familiar terms with the clinical manifestations of the diseases of the endocrine glands requires a working knowledge of the chemistry of the hormones and at least a grasp of the basic principles underlying their assay and the laboratory tests used in determining the functional state of the various glands.

During the last century the clinical features characterizing overfunction or underfunction of the individual glands have been pretty thoroughly described by a long series of able and keen-eyed physicians. Although this process has not been completed—witness the recent description of aldosteronism—it has slowed down and the centre of the stage has been taken over by the biochemist. It is in the laboratory in the last quarter-century and especially in the last 10 years where the tremendous advances have been made in the identification and chemistry of the various hormones, their synthesis and the discovery of analogues.

One of the valuable features of this book to the practising physician and internist is the happy way in which these latter features have been included in detail which is not overwhelming but quite sufficient for those who will not be doing the tests themselves.

The book is basically a clinical one with emphasis on diagnosis and treatment. Each section opens with an introductory account of the physiology and chemistry of the particular gland under study followed by descriptions of the various disease states and their treatment. The section on the highly important adrenal cortex is quite up-to-date and comprehensive but concise.

To the reporter, one of the chief difficulties in endocrinology has been the sorting out of the various types of dwarfism, infantilism and hypogonadism. One of the reasons for this, of course, is that the average internist or general practitioner does not see these patients in any great numbers. In this volume these conditions are extremely well and clearly described and it serves as a valuable reference work in this regard.

There are many black and white illustrations, not all of which show clearly the features intended. Each section is followed by a selected and valuable bibliography.

The book is a product of several of the London hospitals and exemplifies British medical writing in its best tradition, especially the clinical descriptions. It can be heartily recommended for endocrinologists and especially for internists and general practitioners.

THE DESPERATE PEOPLE. Farley Mowat. 305 pp. Illust. Little, Brown and Company, Boston and Toronto, 1959. $5.00.

For centuries, the barren Keewatin plains west of Hudson Bay were the home of a band of inland Eskimos, known as the Ihalmiut, who lived a satisfactory life with the caribou for food and clothing. But the white man came, and as usual the local people suffered. The caribou herds were decimated and by 1947, when Mr. Mowat got to know the remnant of a once proud and happy people, the Ihalmiut were a half-starved collection of persons without a future.

Angered by the indifference of government to their sufferings, Mr. Mowat, who is a man of considerable compassion and insight, wrote a biting piece of polemic called "The People of the Deer", which was dismissed as nonsense by some who should perhaps have checked their facts better. He has now traced the further fate of the Ihalmiut up to the present day, and much of his second book "The Desperate People" does not reflect much credit on the white man. Since the author has now taken a great deal of pains with his documentation, this assault on white Canadian complacency will not be so easy to dismiss as exaggeration.

Fortunately, the powers that be have now apparently discovered that educated Eskimos are just as able to cope with modern technology as we are, and there is some hope that they may be given the opportunities they deserve (and which have already been given them by the enlightened Danes in Greenland).

Mr. Mowat's design in his book is to turn this hope into certainty, and he deserves a fair hearing from intelligent people. The book is not pleasant reading, for it is a history of horrors—starvation, diphtheria, poliomyelitis, suicide and murder—aided and abetted by white pigheadedness, procrastination, prejudice and plain incompetence. The story is very well told indeed, and this reviewer found the book difficult to put down. It is highly recommended to all of the growing band of people whose interest in the Canadian North is not limited to the number of dollars extractable from it.

THEY WHO FOUGHT HERE. Bell Irvin Wiley. 273 pp. Illust. Brett-Macmillan Ltd., Galt, Ontario, 1959. $10.00.

As the centenary of the American Civil war draws near, we may expect a spate of new publications concerning that already well-documented conflict. The conduct of the campaigns, and the personalities of the generals, will be subject to further scrutiny. The book under review, however, deals solely with the day-to-day life of the soldier, his rations, clothing, weapons, health, welfare and morals.

One chapter deals exclusively with the "sick and wounded". The Civil War produced a variety of new weapons. Machine guns, ironclads, even a submarine, were used for the first time in war. There appears to have been no corresponding advance in military medicine and surgery, although both armies had competent medical directors throughout. The importance, for example, of sanitary discipline was recognized, but, especially in the early days of the war, it was never, in either army, effectively enforced. The author suggests that the "low standards and lax practices which characterized young America" may have been a factor. However, as the two vast, hastily raised, armies got into their stride, there was an improvement, as evidenced by a decline in the incidence of "camp fevers" and "continued fevers", presumably the enteric group, from their peak in the autumn of 1861. The value of quinine in the treatment of malaria was recognized. Indeed its use by some Southern doctors to a limited extent as a prophylactic is recorded.

The V.D. rate was high in both armies. Infected camp followers were plentiful. One soldier wrote home from Georgia "there is the most hoars here that I ever saw in my life, boath black and white. I thought that Washington had enough but this beats that." The introduction of chloroform, already used to a limited extent in the Crimea, had removed some of the horror from war surgery. However, even that was denied to the Confederate wounded in the last years of the war, as the blockade took effect.

The author suggests that medical officers were not all highly esteemed, and quotes such sources as a Louisiana private who complained "These damn quacks we have got for Drs. . . . . are doing me more harm than good." Comment of this kind might still be heard in military circles today, and probably should not be taken too seriously. Some chaplains come in for even harsher criticism. They are charged with everything from cowardice to lack of touch with reality. A Union lieutenant tells of one who preached a sermon to the troops on infant baptism, concluding with "an eloquent appeal to mothers", although "there wasn't a mother in the audience, and not more than two or three infants".

The book is lavishly illustrated with excellent contemporary photographs and sketches and, although it will probably add little to the knowledge of the serious medical or military student, it will undoubtedly give pleasure and interest to many.

TEXTBOOK OF PHARMACOLOGY FOR NURSES. Margene O. Faddis and Joseph M. Hayman, Jr., Western Reserve University, Cleveland, Ohio. Supplement on Canadian Drug Legislation by F. Norman Hughes and Isabel E. Stauffer, Faculty of Pharmacy, University of Toronto. 451 + 50 pp. Illust. 5th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1959. $5.50.

The latest revision of the very useful *Textbook of Pharmacology for Nurses* by Faddis and Hayman retains the same organization of material and much of the content of the previous edition. However, the authors have made numerous valuable additions of necessary information on new drugs, many of which nurses are required to administer.

The first four chapters are extremely helpful in introducing the study of drugs and their administration. The many tables and diagrams here are excellent teaching aids. The content which deals with the therapeutic agents is concise and simple but pertinent.

The supplement on Canadian drug legislation is indeed welcomed in Canada. This material has not previously been so readily available to nurses in such a complete and succinct form. The increasing complexity of drug therapy and the ever increasing problem of self-medication, with the many current publications on drugs, necessitates on the part of the nurse a knowledge of the controls maintained for protection of the public. Professor Stauffer and Dean Hughes are to be commended for this timely and valuable contribution.

(Continued on page 401)

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NEUROTISCHE DEPRESSION (Neurotic Depression). H. Voelkel. 116 pp. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1959. $3.80.

A precise definition of neurotic depression cannot be given with our present knowledge in this field. However, clinical and therapeutic needs require its differentiation from both the manic depression and the reactive depression. The main causation of the neurotic depression appears to be in the genetic and environmental influences during the earlier stages of life although it is not possible to ascribe the condition to any specific event. The clinical picture is well illustrated in this study by a number of extensive case histories. The author's approach to understanding the pathogenesis of the condition is virtually eclectic, although a basic concept used as the centre of the developing condition is Störring's "crystallization nuclei". The therapeutic approach is likewise multiform. Debatable as this presentation may be, this study has the definite merit of dealing with a problem coming to the fore in our present-day preoccupations.

CHILDREN IN PRACTICE. John Peterson. 227 pp. Cambridge University Press; The Macmillan Company of Canada Limited, Toronto, 1959. $4.25.

Mr. Peterson, who is warden of University House, Bethnal Green, London, England, states that his purpose in writing this book is to assist medical students to see their patients within their social context rather than as a disease entity and to indicate to students what others are doing for children in our society. The book is divided into ten chapters, of which the sixth, on the physician and child, is the centre of the book. The chapters preceding this are preparatory and deal with the larger notions of the environment, aiming to get the doctor to the position where he may see the child in perspective within his environmental contacts. The first chapter on the physician and his environment defines the sphere of practice of the physician. Chapter 2 on the physician and the neighbourhood deals with problems of urban and rural practice. Chapter 3 describes the child's adaptation to his neighbourhood, and chapter 4 the demands of the neighbourhood and school upon the child. Chapter 5 discusses discipline and the child.

Chapter 6, which is the centre of the book, attempts to describe pitfalls and limitations in understanding the child. Chapter 7 describes the exceptional home. Chapter 8, on the infant in his home, gives an account of the maternity and child welfare services and their intention and development. Chapter 9, on the child at school, is an account of day nursery and nursery school and some of the problems which face educational authorities. The tenth and last chapter, on the handicapped child, covers chiefly the problem of the retarded child.

Mr. Peterson's idea in writing a book, in order to acquaint the medical student and practitioner with the background of the child other than his medical illnesses, is a very good one, but the book is very difficult to read, lacks interest and depth and on the whole is most uninspiring. The material is not well presented; it is difficult to maintain interest while reading, and the author skips from one thought to another without much rhyme or reason. If the medical student were able to finish this book, he would not be much more enlightened than before starting it.

DIE BEGINNENDE SCHIZOPHRENIE: VERSUCH EINER GESTALTANALYSE DES WAHNS (Early Schizophrenia: An Attempt at Gestalt Analysis of the Delusional State). K. Conrad, University of Göttingen. 165 pp. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1958. $4.25.

This monograph is an excellent phenomenological study of early schizophrenia. It was based on 117 patients, all of whom were soldiers in service, breaking down within a one-year period during the Second World War. This relative homogenicity of the patients and their environmental exposure offered a uniform setting, rarely available for clinical studies. Although this book is the result of research during the war, it is clinically oriented with no direct implications for military psychiatry.

The central theme in this work is the analysis of the *specific* schizophrenic experience as obtainable from the patient, in its relationship to the patient's total life experience. The monograph however goes further than that, for it gives a fairly complete presentation of the phenomenology of the acute and subacute schizophrenic episode.

The author divides into distinct phases the sequence of symptoms emerging during the progress of a schizophrenic breakdown. Each of these phases is described in scholarly fashion in separate chapters of the monograph, amply documented with case histories. The prodromal phase (irritability, anxiety, depression, premonitions, etc.) is followed by the "apophænic" phase, characterized by rather specific delusions, illusions or hallucinations, with however the personality still essentially coherent. This is followed by the "apocalyptic" phase in which disintegration of the personality occurs, often manifested outwardly by catatonic phenomena. The last phase is a consolidation of symptoms into a chronic "defect" state, or a more or less successful reintegration of the personality. These phases when all present serve as an "ideal model" for the march of events during the acute or subacute schizophrenic breakdown. The second part of this monograph describes different and rather distinct types of the schizophrenic episode as deviations from the "ideal model". An attempt is also made to correlate these types with the conventional subgroups of schizophrenia (i.e. paranoid, catatonic, etc.). Finally an appendix deals with non-schizophrenic delusional states, and with a criticism of the unwarranted extension of the concept of schizophrenia by some authors.

Readers trained exclusively in a psychodynamically oriented psychiatry will find a rather alien frame of reference in this monograph. It will also disappoint those who expect a "Gestalt" analysis in the recent existentialistic sense. This study is based on the concepts of the classical German psychopathological school originated by Jaspers. The author himself points out in his "Summary and Outlook" that this study is a link with the past and not a further elaboration of present-day trends. However, even with its conservative ties this work is a fresh departure, and it presents original ideas in a very readable form. It is recommended to those with a special interest in schizophrenia rather than to the general reader.

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FORTHCOMING MEETINGS

CANADA

COLLEGE OF GENERAL PRACTICE OF CANADA, Fourth Annual Scientific Assembly, Montreal, Que. (Dr. W. V. Johnston, Executive Director, 176 St. George Street, Toronto 5, Ont.) February 29-March 3, 1960.

SECTION OF GENERAL PRACTICE, B.C. DIVISION, CANADIAN MEDICAL ASSOCIATION, Eighth Annual Scientific Session, Harrison Hot Springs Hotel, Harrison, B.C. (In charge of registration: Dr. R. A. White, Oliver, B.C.) March 30-April 2, 1960.

ONTARIO CHAPTER, COLLEGE OF GENERAL PRACTICE OF CANADA, Annual Clinic Day, Kitchener, Ont. (Dr. N. R. McMurchy, Publicity Chairman, 215 Frederick St., Kitchener, Ont.) April 6, 1959.

CANADIAN ANÆSTHETISTS' SOCIETY, Western Divisional Meeting, Victoria, B.C. (Dr. W. L. Esdale, Secretary-Treasurer, B.C. Division, Canadian Anæsthetists' Society, 7476 Inverness St., Vancouver.) April 28-30, 1960.

ONTARIO MEDICAL ASSOCIATION, 80th Annual Meeting, Toronto, Ont. (Dr. Glenn Sawyer, General Secretary, 244 St. George Street, Toronto 5, Ont.) May 9-13, 1960.

CANADIAN PUBLIC HEALTH ASSOCIATION, 48th Annual Meeting, Halifax, N.S. (Dr. G. W. O. Moss, Honorary Secretary, 150 College Street, Toronto 5, Ont.) May 31-June 2, 1960.

CANADIAN FEDERATION OF BIOLOGICAL SOCIETIES (comprising the Canadian Physiological Society, the Pharmacological Society of Canada, the Canadian Association of Anatomists and the Canadian Biochemical Society), Third Annual Meeting, Winnipeg, Man. (Dr. E. H. Bensley, Honorary Secretary, Montreal General Hospital, 1650 Cedar Ave., Montreal 25, Que.) June 8-10, 1960.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Jasper Park Lodge, Jasper National Park, Alberta. (Dr. Donald M. MacRae, Secretary, 324 Spring Garden Road, Halifax, N.S.) June 10-12, 1960.

CANADIAN MEDICAL ASSOCIATION, 93rd Annual Meeting, Banff, Alberta. (Dr. A. D. Kelly, General Secretary, C.M.A. House, 150 St. George Street, Toronto 5, Ont.) June 13-17, 1960.

2ND WORLD CONGRESS OF THE WORLD FEDERATION OF SOCIETIES OF ANÆSTHESIOLOGISTS, Toronto, Ont. (Dr. R. A. Gordon, Chairman of Organizing Committee, 178 St. George Street, Toronto 5, Ont.) September 4-10, 1960.

UNITED STATES

AMERICAN COLLEGE OF ALLERGISTS, Sixteenth Congress and Graduate Instructional Course in Allergy, American Hotel, Bal Harbor, Miami Beach, Florida. (American College of Allergists, 2049 Broadway, Boulder, Colorado, U.S.A.) February 28-March 4, 1960.

7TH INTERNATIONAL ANATOMICAL CONGRESS, New York. (Dr. D. W. Fawcett, Executive Secretary, Department of Anatomy, Cornell University Medical College, 1300 York Ave., New York 21, N.Y.) April 11-16, 1960.

SOCIETY OF AMERICAN BACTERIOLOGISTS, 60th Annual Meeting, Philadelphia, Pa. May 1-5, 1960.

NATIONAL TUBERCULOSIS ASSOCIATION, Annual Meeting, in conjunction with the American Trudeau Society, Los Angeles, Calif. (Sol S. Lifson, Director, Education and Public Relations, National Tuberculosis Association, 1790 Broadway, New York 19, N.Y.) May 16-18, 1960.

OTHER COUNTRIES

FIRST BAHAMAS ALLERGY CONFERENCE, Nassau Beach Lodge, Nassau Bahamas. (Dr. B. L. Frank, Organizing Physician, Bahamas Conferences, P.O. Box 4037, Fort Lauderdale, Florida.) March 5-12, 1960.

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CUSHING'S SYNDROME: DIFFERENTIAL DIAGNOSIS AND COMPLICATIONS

Cushing's syndrome is potentially fatal. Its protean effects are to a certain extent proportional to the length of time it has been present. Consequently it is important to diagnose this condition as soon as evidence of its presence appears. The classical clinical picture of this disease and the differential diagnosis described in texts pertain to advanced or extremely late stages. The initial symptoms and signs in 34 cases were evaluated by Hurxthal and O'Sullivan (*Ann. Int. Med.*, 51: 1, 1959) to determine whether or not they could possibly be of value in promoting more prompt diagnosis. Contrary to opinions held in the past, it was established that the onset was rapid in 71% of cases, and that this did not necessarily mirror the underlying pathological condition.

The term "rapid onset" was defined as that observed in cases where the symptoms were sufficiently dramatic to warn the patient, as well as the physician, of its presence. Facial œdema, with or without œdema of the lower extremities, was the most common initial sign in this group. This brought about consideration of a diagnosis of hypothyroidism, nephritis or nephrosis, or allergic or cardiac disease. The occurrence of a rapid gain in weight has been frequently explained on the basis of simple obesity, even though additional signs such as amenorrhœa or hirsuitism should have been recognized as diagnostic features. Thyroid parameters are usually conflicting but when they are considered individually in the absence of weight loss, nervousness and increased perspiration, they may support the diagnosis of hypothyroidism. Renal colic can also be the first clinical sign and may be responsible for the erroneous diagnosis of idiopathic renal calculus formation. Furthermore, psychoses occur in the more severe cases and such patients should be examined for other indications of Cushing's syndrome.

When illness begins insidiously —in such cases one speaks of a "gradual onset"—a list of the individual manifestations of Cushing's syndrome that can be attri-

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buted to other diseases is taken into consideration in the differential diagnosis. These manifestations include simple obesity, familial hirsutism, psychogenic or emotional amenorrhœa, postmenopausal or senile osteoporosis, hyperparathyroidism, essential hypertension, diabetes mellitus, polycythæmia, purpura and mental disturbances.

In the course of time, its effect on calcium and protein metabolism can be responsible for pathological factors and renal calculi. Hypertension can be a continuing problem, even when the underlying pathological state has been treated adequately. The well-known susceptibility to infections which characterizes these patients is especially emphasized. Peptic ulcerations occurred in 9% of these patients, but this incidence does not exceed that found in the general population. Finally, the appearance of multiple peripheral neuritis in three of the cases in this series is mentioned. The symptoms and signs were not dissimilar to those seen in the Guillain-Barré syndrome or in diabetic neuropathy.

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MUCOCUTANEOUS LESIONS OF REITER'S SYNDROME

The high incidence of mucous membrane lesions in patients with Reiter's syndrome (80% in a series of 38 patients) is not generally appreciated, according to Montgomery *et al.* (*Ann. Int. Med.*, 51: 99, 1959). About half of the patients with painless genital lesions also have characteristic painless oral mucosal lesions. The keratosis of Reiter's syndrome, present in 11 of 38 patients (an incidence of about 30%), is, they believe, identical with what has been called keratodermia blennorrhagica. These lesions are uninfluenced by antibiotics or corticosteroids.

Mucocutaneous lesions may be as important in establishing the diagnosis of Reiter's syndrome as is nonspecific urethritis or conjunctivitis. In equivocal cases, when neither urethritis nor conjunctivitis has been observed or well documented, or in the incomplete form of the syndrome, the mucocutaneous lesions, known to appear four to six weeks after the onset, may be diagnostic. In the endemic form, the triad of Reiter's syndrome might better be considered a tetrad, consisting in its complete form of urethritis, conjunctivitis, arthritis and mucocutaneous lesions.

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GENETIC FACTORS IN PREDISPOSITION TO PERNICIOUS ANÆMIA

Although many observations suggest that there is a genetically determined predisposition to the development of pernicious anæmia, family studies have not been adequate to confirm this. Studies relating to other predisposing factors have also complicated matters. A more direct approach to the question of genetic factors in pernicious anæmia can be provided by studying the ability of relatives of patients with pernicious anæmia to absorb vitamin B_{12}. A study by McIntyre and his colleagues (*Bull. Johns Hopkins Hosp.*, 104: 309, 1959) reports the examination of 106 relatives of 34 patients with well-documented and undoubted pernicious anæmia. A control group of 97 normal persons not known to be related to patients with pernicious anæmia was used for comparison. The modification of the urinary excretion method (Schilling) was used to estimate the ability of subjects to absorb radioactive vitamin B_{12}. Hæmatocrit value and ABO blood types were determined on blood from many of the family members and the tubeless gastric analysis was performed on 86. Among the relatives of patients with pernicious anæmia there were 21 whose excretion values for radioactive vitamin B_{12} were less than 12.5% and 19 had 12.5 to 15%. Among the normal controls there was only one in the less than 12.5% group and seven excreted 12.5 to 15%. Fifteen of the 86 family members tested by the tubeless method had achlorhydria, which was confirmed in ten by gastric intubation. No new cases of pernicious anæmia were discovered on this examination and only one case of hypochromic anæmia was encountered. Among the patients with pernicious anæmia and members of their families there appears to be a trend towards a higher than normal percentage of those with blood group A. The authors discuss the

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findings and believe that their data indicate that predisposition to pernicious anæmia is inherited, most probably as the effect of a single dominant autosomal factor. The value to clinical medicine of detecting carriers of inherited diseases is re-emphasized. The hope is expressed that it will become easier to determine the exact nature of the genetic block, the basic nature of the "inborn error of metabolism" in carriers of this gene.

FERTILITY AFTER CERVICAL DILATATION

In the nineteenth century, one of the methods extolled for curing infertility was simple dilatation of the cervix. In a recent article (*Am. J. Obst. & Gynec.*, 78: 974, 1959) Javert of New York complains that this simple method is no longer popular, and describes a series of 180 private patients treated for infertility by dilatation of the cervix in the office either as a primary procedure or as follow-up measure to a hospital procedure. He states that there were 158 infertile women in this group, of whom 66 or 41.8% conceived after cervical dilatations. Conception occurred within a month of dilatation in 39 or 59% of cases, and Javert considers that in these the procedure should be given most of the credit. This rate is almost twice as good as the success of 30% found by other writers in a larger series of planned pregnancies in fertile couples, and of 10% after a simple bimanual pelvic examination.

The author considers that 35 of the patients had a cervical stenosis and 31 of these became pregnant after dilatation; however, another 35 patients without stenosis also became pregnant. In discussion of the paper, Israel of Philadelphia casts great doubt on the efficacy of the procedure, pointing out that the psychosomatic effects of being well attended medically or being exposed to an arresting new manœuvre cannot be evaluated accurately in sterility. He also notes that the patients had other "therapy", including a recommendation of the knee-chest posture for intercourse. Henriksen of Los Angeles, who was somewhat less sceptical, pointed out that we should not always take the credit for what nature frequently accomplishes, despite interference by man which is often both ill advised and bungling. He also mentioned that the question whether we should labour to increase the human fertility curve or to depress it was receiving much space at the moment. He added that "it is distressingly clear that man is going all out to make the age-old physiologic act of bearing children most difficult", and finished his discussion by saying "it is well to be humble with the awareness that women have been conceiving from time immemorial and that each era of the past, self-satisfied with its acclaimed knowledge, has been contented with its modus operandi and its results".

INTRACRANIAL DERMOID AND EPIDERMOID TUMOURS

Intracranial dermoids and epidermoids, although benign, often remain undiagnosed until their size and spread make a complete

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removal impossible. Ross Fleming and Botterell of Toronto (*Surg. Gynec. & Obst.*, 109: 403, 1959) review the pathology of these tumours, report illustrative cases and present a follow-up study of 27 patients operated on at the Toronto General Hospital between 1929 and 1956.

Intracranial dermoids and epidermoids produce symptoms by slowly compressing and destroying adjacent structures as they gradually enlarge. The clinical picture may be one of local disturbance of function with focal neurological signs, or general increase in intracranial pressure. In half the present series headaches were noted but papilloedema was confined to two cases. Focal neurological signs, which were common, varied from visual field changes and epilepsy to hemiplegia, cranial nerve lesions and cerebellar signs. Proptosis was invariably associated with anterior temporal and frontal epidermoids invading the orbit. The age at onset of symptoms was between 15 and 40 in most cases, but the tumour may remain silent until much later or be found incidentally at autopsy. Dermoids tend to appear earlier than epidermoids. In most cases, symptoms preceded diagnosis by several years. Where the skull was involved, a characteristic roentgenographic appearance was seen, consisting of a central area of radiolucency surrounded by a definite margin of condensed sclerotic bone. Radiologically visible calcification was rare.

In the Toronto series, epidermoids were twice as common as dermoids and had a tendency to occur laterally, while dermoids were more commonly situated in the midline. The majority of patients are permanently cured by complete removal of the tumour, but this may prove extremely difficult; incomplete removal may render the patient free from symptoms for many years.

THE NEW MEMORIAL HOSPITAL OF LONG BEACH, CALIFORNIA

The Second Annual Scientific Symposium of the Medical Staff of the new Memorial Hospital of Long Beach, California, will be held on May 4, 1960, at the new 400-bed hospital facility, 2801 Atlantic Avenue, in conjunction with its formal opening. (This is a change from the previously announced date of December 2, 1959, occasioned by construction delays.)

The theme of the Symposium this year will be "New horizons in medicine". Frank Gerbode, M.D., Associate Professor of Surgery, Stanford University School of Medicine, will be one of the principal speakers.

Inquiries should be addressed to: George X. Trimble, M.D., Director of Medical Education, Seaside Memorial Hospital of Long Beach, Long Beach, California.

ACUTE PERICARDIAL FAT NECROSIS

Acute pericardial fat necrosis is a recently described clinico-pathological entity consisting of acute onset of precordial pain, pleuritic pain in the left chest radiating to the left shoulder, and the demonstration of a juxtacardiac mass on the chest radiograph. Tomograms of the juxtacardiac mass in a patient of Chester and Tully (*J. Thoracic Surg.*, 38: 62, 1959) revealed several ovoid areas of decreased density. Because of these findings and of persisting pain in the left chest, an exploratory operation was performed through a left anterolateral incision in the sixth intercostal space. A firm ovoid mass identified as a pericardial fat pad was excised. The etiology of this condition is not clear; some have emphasized constitutional factors (obesity), but in this case the authors suggested that a severe lifting effort was the major cause. This condition may be entertained in the differential diagnosis of acute myocardial infarction, pulmonary embolism, hæmorrhage into a neoplasm of the lung, and primary metastatic carcinoma of the lung.

IS ATHEROSCLEROSIS DUE TO DEFICIENCY OF ESSENTIAL FATTY ACIDS?

Although investigations over the last four or five years suggest that unsaturated fatty acids tend to prevent hypercholesterolæmia and that diets containing different kinds of fat will raise the serum-cholesterol level, there is no conclusive evidence from these findings that atherosclerosis is a consequence of fatty-acid deficiency. Malmros and Wigand (Lund, Sweden) recall the work of Anitschkow and other Russian investigators who produced atherosclerosis in rabbits on a high cholesterol, high fat diet. When the animals were given the sunflower-seed oil alone without the addition of cholesterol, no atheromatous lesions developed (*Lancet*, 2: 749, 1959).

After experiments by other workers which showed that hyperlipæmia and atherosclerosis can be produced in rabbits by diets which contain no cholesterol but such fat as peanut or coconut oil, Malmros and Wigand developed a semisynthetic cholesterol-free diet in which fat was present in 8% concentration. The fat content was varied in different experiments and it was found that milk fat and hydrogenated coconut fat produced both hypercholesterolæmia and, within three to four months, gross changes of a type seen in cholesterol-induced atherosclerosis in the aorta. Corn oil, cottonseed oil, poppyseed oil, groundnut oil, and rapeseed oil produced only a small rise in serum cholesterol and, after four months, no gross lesions in the aorta. Replacing hydrogenated coconut fat by corn oil caused an abrupt fall in serum cholesterol.

These findings suggest either that coconut fat contains some atherogenic factor or that it is deficient in essential fatty acids. Coconut fat contains only 1% linoleic acid and even that is destroyed if the fat is hydrogenated. The addition of corn oil or linoleic acid in 4% concentration to their semisynthetic diet diminishes even though it does not abolish the hypercholesterolæmia produced by the addition of 8%

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Canad. M. A. J.
Feb. 13, 1960, vol. 82

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PROOF —SAFETY—ECG EVIDENCE[8]

Human I.V. Studies with Tenuate 10 mg., IV equiv. of 100 mg. oral dose (4 times recommended dose)

				Blood Pressure		ECG	
Patients	Sex	Age	Diagnosis	Before Inj.	After Inj.*	Control	After Inj.
E. M.	F	62	Diabetes mellitus. A.S.H.D., compensated. Obesity, postmenopausal.	125/54	116/52	Sinus rhythm. Nonspecific myocardial changes.	No change
F. S.	M	67	A.S.H.D., mild hypertension. Early congestive cardiac failure.	175/90	175/90	Sinus rhythm. Early LVH.	No change
M. A.	F	68	Essential hypertension. Degenerative osteoarthritis. Obesity.	207/104	194/98	Sinus rhythm. Normal tracing.	No change
S. G.	M	30	Normal subject.	126/74	122/78	Sinus rhythm. Normal tracing.	No change
D. A.	M	33	Normal subject.	112/80	121/90	Sinus rhythm. Normal tracing.	No change

*This represents the averages of the readings taken at 30-second and 1-minute intervals for 5 minutes prior to injection and 5 minutes after injection of the drug. The amount of fluctuation was considered insignificant.

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of glyceryl trilaurate. When seven rabbits were given the semisynthetic diet without any fat whatsoever, their serum-cholesterol levels nevertheless rose regularly. Twenty-one weeks after the beginning of the experiment, the aorta of one rabbit showed the same atheromatous plaques as in cholesterol-induced atherosclerosis. One of the animals was given 8% corn oil, after having been on this fat-free diet for 24 weeks, and his serum cholesterol level fell promptly from the high levels of 300 mg. % to 150 and 100.

These experiments were carried out on fully grown rabbits, and whether the findings can be applied to man is still an open question. Malmros and Wigand believe that there may not be much difference between the reactions of man and of rabbit. It may depend on the kind of diet we usually eat. If our diet includes relatively large amounts of milk fat and other animal fat, coconut fat and hydrogenated fat, the relatively small amounts of polyunsaturated fatty acids which we take in at the same time will not suffice to prevent hypercholesterolæmia. Full-blown deficiency of essential fatty acids was not produced in these experiments but, if hypercholesterolæmia and subsequent atherosclerosis is one manifestation of deficiency, then it can be produced easily in full-grown rabbits without eliminating all the polyunsaturated fatty acids, provided fat, such as butter containing saturated fatty acids in excess, is included in the

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diet. The same may hold for man. In summary, then, these authors believe that a relative deficiency of essential fatty acids, due to the large intake of an unbalanced high fat diet, may cause atherosclerosis in man.

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CADAVER BLOOD

It is well known that in Russia cadaver blood is used for blood transfusions rather than donor blood. In consequence, lay persons often ask whether it would be possible to substitute a system of collecting cadaver blood for some of the blood donor clinics in North America.

This question is dealt with in an answer to a correspondent in the *Journal of the American Medical Association* (171: 2153, 1959). The expert who answers the question says that cadaver blood for transfusion purposes has attracted some attention in the United States but has never gained acceptance for a number of reasons. The objections to its use include a preference for blood from a living donor, the legal questions involved in taking blood from a cadaver, the difficulty of avoiding bacterial contamination of cadaver blood, the uncertainty of the source of supply (this is particularly stressed because in the Soviet Union only the cadavers of those dying in emergencies such as coronary occlusion, cerebral vascular accidents and severe injury are used), the need for facilities and personnel to collect blood from suitable and available cadavers, and the availability of a history of previous good health from a live donor in contrast to the inadequate history in the case of a cadaver.

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EFFECTIVENESS OF AN ORAL CONTRACEPTIVE

A norethynodrel-œstrogen combination was tested as an oral contraceptive. The results of four projects carried out in the West Indies on 830 subjects who took the medication for a total of 8133 menstrual cycles or 635 woman-years are reported by Pincus and co-workers (*Science*, 130: 81, 1959). One tablet (10 mg. of norethynodrel plus 0.15 mg. of ethinyl œstradiol 3-methyl ether) was administered daily from the fifth to the twenty-fourth day of the menstrual cycle. One probable pregnancy and sixteen certain pregnancies occurred in women taking the medication. But it was clear from the tabulated data that the rate of conception was proportional to the number of tablets missed.

The side reactions were similar to those common in early pregnancy; the incidence of breakthrough bleeding was 2% of the cycles. The acceptability of this method of contraception may be found by listing the reasons given for withdrawal. Side reactions and lack of interest accounted for 30-50% of the withdrawals. An antacid or placebo was found to relieve up to 90% of these side effects. Lack of interest was found to be due chiefly to lack of motivation among an economically low-level group. In one of the projects, availability of sterilization, frequent moving and improvement in economic situation accounted for high withdrawal rates.

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SEMINAR ON SCHEDULE OF IMMUNIZATION

A meeting held at the International Children's Centre, in October, 1959, in Paris, and attended by pædiatricians, public health physicians, bacteriologists and immunologists, proposed to define the theoretical bases for establishing a schedule of vaccinations, and with this end in view, to consider the known facts and the new data concerning neonatal passive immunization; the capacity of the young child to become immunized; the modes, possibilities and possible disadvantages of associated or combined vaccines; the problems raised by repeat injections and their timing; and the need for booster vaccinations.

The first report was devoted to the transfer of immunity from the mother to the child through the transplacental route and by breast feeding. In man, in contrast to other species, the transfer occurs through the placenta and not through the milk or the colostrum. The phenomenon is a complex and selective one involving the size and shape of antibody molecules and probably the direct action of the placenta. The amniotic fluid might play a role. These facts explain these differences: the satisfactory transfer of antidiphtheritic, antitetanic and antiviral antibodies, the less satisfactory transfer of protection against pertussis, and the very poor transfer of typhoid H agglutinins and of agglutinins against *E. coli*. The immunity conferred through that route depends essentially on maternal immunity (epidemiological conditions and vaccinations of the mother).

Development of the aptitude for active immunity in the newborn and the infant was next considered. It was recalled that the ability of the newborn to produce antibodies is slight. The passive antibodies transmitted by the mother constitute a variable obstacle to active immunization according to their nature, and above all according to the power of the antigen used. Very diverse results had been obtained by vaccinations performed during the first weeks of life.

It was reported that the addition of poliomyelitis vaccine does not change the response to the three other antigens. However, the fourfold vaccine raises problems of preservation at a low temperature. In the final discussion of the schedule proper, emphasis was laid on the importance of booster injections during the second year of life.

A NEW NONAMPHETAMINE ANORECTIC AGENT

A new nonamphetamine-long-acting anorectic drug, 2-phenyl-tert.-butylamine resin (Ionamin), was administered to 178 patients for purpose of weight reduction. A total of 2587 patient-days' experience with Ionamin was clinically evaluated by Freed and Hays (*Am. J. M. Sc.*, 238: 55, 1959). Weight loss was approximately 0.25 lb. per patient per day. This new drug effectively suppresses appetite and does so with a significantly reduced incidence of side effects from that found with equivalent therapeutic doses of amphetamine. Individuals whose weight had reached a plateau with other anorexigenic agents have responded satisfactorily to this agent.